PROTOCOL UP0057

AN OPEN-LABEL, FIXED-SEQUENCE STUDY IN HEALTHY STUDY PARTICIPANTS TO EVALUATE THE EFFECT OF COADMINISTERED ERYTHROMYCIN ON THE PHARMACOKINETICS AND SAFETY OF PADSEVONIL

PHASE 1

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SERIOUS ADVERSE EVENT REPORTING

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ADaM	analysis data model
AE	adverse event
AED	antiepileptic drug
ALP	alkaline phosphatase
ALT	alanine aminotransferase
ANOVA	analysis of variance
AR	adverse reaction
AST	aspartate aminotransferase
BMI	body mass index
BP	blood pressure
BZD	benzodiazepine
cBZR	central benzodiazepine receptor
CDMS	clinical data management system
CI	confidence interval
CNS	central nervous system
CPMP	Committee for Proprietary Medicinal Products
CRO	contract research organization
C-SSRS	Columbia-Suicide Severity Rating Scale
CYP	cytochrome P450
DBP	diastolic blood pressure
DDI	drug-drug interaction
ECG	electrocardiogram
eCRF	electronic Case Report form
ES	Enrolled Set
EOS	End of Study
EudraCT	European Union Drug Regulating Authorities Clinical Trials
FAS	Full Analysis Set
$GABA_A$	gamma-aminobutyric acid type A
GCP	Good Clinical Practice
GMP	Good Manufacturing Practice
HBsAg	hepatitis B surface antigen
HCV-Ab	hepatitis C virus antibody
HIV	human immunodeficiency virus

IB	Investigator's Brochure
ICF	Informed Consent form
ICH	International Council for Harmonisation
IEC	Independent Ethics Committee
ILAE	International League Against Epilepsy
IMP	investigational medicinal product
IUD	intrauterine device
IUS	intrauterine hormone-releasing system
LEV	levetiracetam
LLOQ	lower limit of quantification
MHRA	Medicines and Healthcare products Regulatory Agency
NCA	noncompartmental analysis
OLE	open-label extension
OTC	over-the-counter
PD	pharmacodynamics(s)
PDILI	potential drug-induced liver injury
PET	positron-emission tomography
PI	Principal Investigator
PK	pharmacokinetic(s)
PK-PPS	Pharmacokinetic Per-Protocol Set
PS	Patient Safety
PSL	Padsevonil
QTcB	QT interval corrected for heart rate using Bazett's formula
QTcF	QT interval corrected for heart rate using Fridericia's formula
REC	Research Ethics Committee
SAE	serious adverse event
SAP	Statistical Analysis Plan
SBP	systolic blood pressure
SD	standard deviation
SFU	Safety Follow-up
SOP	Standard Operating Procedure
SV2	synaptic vesicle 2
TEAE	treatment-emergent adverse event
ULN	upper limit of normal

1 SUMMARY

Padsevonil (PSL, previously known as UCB0942) is a novel chemical entity with selective dual synaptic vesicle protein 2 (SV2) and central benzodiazepine receptor (cBZR) site affinity. It is currently being proposed initially for the treatment of focal-onset seizures in adult patients with drug-resistant epilepsy.

Many antiepileptic drugs (AEDs) are associated with drug-drug interactions (DDIs). Preclinical data indicate that PSL metabolism is mediated mainly by cytochrome P450 (CYP) 3A4 with minor involvement of CYP2C19. Consequently, PSL exposure may be altered by CYP3A4 inhibitors. It has already been demonstrated that concomitant administration of a strong CYP3A4 inducer (carbamazepine, UP0002) significantly reduces exposure to PSL.

UP0057 is a Phase 1, open-label, fixed-sequence study in healthy study participants to evaluate the effect of a coadministered moderate CYP3A4 inhibitor (erythromycin) on the pharmacokinetics (PK) and safety of PSL.

The primary objective of UP0057 is to evaluate and compare the plasma PK of PSL in the presence and absence of erythromycin in healthy study participants. The secondary objectives include the following in healthy study participants: to assess safety and tolerability of PSL in the presence and absence of erythromycin; to evaluate and compare the plasma PK of PSL metabolites in the presence and absence of erythromycin; and to assess and compare the urine PK of PSL and its metabolites in the presence and absence of erythromycin. The exploratory objectives are to estimate the inter- and intra-study participant variability in the plasma PK of PSL and its metabolites, to evaluate and compare the venous blood and MITRA microsampling PK of PSL and its metabolite in the presence and absence of erythromycin, and to archive blood samples for genotyping of drug metabolizing enzymes and biomarkers.

UP0057 is comprised of the following periods: a Screening Period; 3 Treatment Periods, and a Safety Follow-Up (SFU) Period. The Screening Period will occur within 28 days prior to the start of Treatment Period 1. Treatment Period 1 and Treatment Period 2 each consist of 5 days of PSL treatment followed by 1-week of wash-out. Treatment Period 3 consists of erythromycin only for 3 days (Treatment Period 3a), erythromycin and PSL for 8 days (Treatment Period 3b), and erythromycin only for 4 days (Treatment Period 3c). The SFU Period is performed 7 to 10 days after the last dose of investigational medicinal product (IMP) or upon discontinuation of the study.

2 INTRODUCTION

2.1 Background

The International League Against Epilepsy (ILAE) defines drug resistance as failure of adequate studies of 2 tolerated and appropriately chosen AEDs either as monotherapy or in combination to achieve sustained seizure freedom (ILAE Classification of Epileptic Seizures, 1981). In the US, there are 3 million adults with active epilepsy (Zack and Kobau, 2017). Assuming epilepsy with focal-onset seizures in 60% of patients and resistance to AEDs in 20% to 40% of patients in the US, approximately 360,000 to 720,000 adult patients with active epilepsy in the US suffer from drug-resistant epilepsy (Giussani et al, 2016; Kwan and Sander, 2004; Semah et al, 1998). It is this drug-resistant epilepsy population that represents the greatest burden of disease for individuals, physicians, and the healthcare system.

A treatment that provides a significant reduction in seizure frequency will reduce mortality (Laxer et al, 2014) and significantly improve quality of life (Choi et al, 2014; Baker et al, 1997) by increasing patients' ability to attain basic safety, freedom from the risk of falls and injuries, and reach the milestones that most people take for granted: a feeling of belonging and social integration; the ability to form intimate relationships and a family; and having a productive and rewarding profession; or other means of self-realization.

Padsevonil is a novel chemical entity currently being developed clinically for the treatment of focal-onset seizures in adult patients with drug-resistant epilepsy. The mechanism of action for PSL is unique in comparison to available AEDs because it has selective affinity both for presynaptic SV2 proteins and for postsynaptic cBZR sites on the gamma-aminobutyric acid type A ($GABA_A$) receptor. At presynaptic sites, PSL binds with high affinity to all 3 subtypes of the human SV2 protein (ie, SV2A, SV2B, and SV2C), and at postsynaptic sites, acts as a partial agonist, binding with moderate affinity to the cBZR sites. Whereas SV2A ligands are characterized by broad-spectrum anticonvulsant activity, $GABA_A$ receptors mediate inhibitory neurotransmission, and their allosteric modulation by cBZR sites offers robust protection against seizures.

The synergistic anticonvulsive effect observed when combining levetiracetam (LEV), an AED that binds with SV2A, with benzodiazepines (BZDs) in preclinical models (Kaminski et al, 2009) was the motivation that led to the design of PSL. In nonclinical studies, PSL administered as a monotherapy has shown higher efficacy than LEV combined with a BZD (diazepam) at matching in vivo occupancies of SV2A and cBZR, respectively. This suggests that PSL's preclinical efficacy is not only due to the combination of these 2 mechanisms of action, but that a unique interaction of PSL with SV2 proteins may also play a role.

Padsevonil is cleared via metabolism involving the CYP pathway; the formation of the 2 major metabolites, [redacted] and [redacted], is mainly mediated by CYP3A4, with potential involvement of CYP2C19. Padsevonil was also found to be a weak mechanism-based inhibitor of CYP2C19. It has been observed that PSL clearance decreased following repeated oral administration, probably as a result of the auto-inhibition of CYP2C19. Consequently, CYP3A4 is assumed to be the main enzyme involved in the metabolism of PSL at steady-state.

Recent studies in patients with refractory epilepsy showed that more than 60% of patients were treated concomitantly with 2 or more AEDs (Johannessen and Landmark, 2010). Drug-drug interactions that result in alterations in the PK of AEDs can have a profound impact on tolerability, efficacy, and safety, and can potentially result in toxicity. It is therefore important to consider and estimate at an early stage the possible interactions that may occur with the concomitant use of PSL and other drugs.

This study will evaluate the impact of a moderate CYP3A4 inhibitor, erythromycin, on the PK, safety, and tolerability of PSL and its metabolites [redacted] in healthy study participants.

2.2 Clinical studies and adverse event profile

As of 01 December 2017, PSL has been administered in 7 completed human Phase 1 pharmacology studies (N01360, N01383, N01386, UP0001, UP0002, UP0010, and UP0013) and 1 completed Phase 2 proof of concept study (EP0069). There are also 2 ongoing Phase 1 clinical

pharmacology studies (UP0036 and UP0039) and 1 ongoing Phase 2 open-label extension study (EP0073). These studies have investigated the safety, PK, and pharmacodynamics (PD) of single and multiple ascending doses of PSL, and the potential interaction of PSL with food, valproic acid, carbamazepine, and other AEDs. Position-emission tomography (PET) investigations have been performed to evaluate the $GABA_A$ receptor occupancy at 2 steady state PSL dose levels and SV2A occupancy at different single PSL dose levels and times postdose in healthy study participants.

In the PSL Phase 1 program completed thus far, 129 healthy study participants and 20 study participants with epilepsy (male and female) have been exposed to PSL at single doses up to 490mg (26 healthy study participants) and repeated doses up to 400mg bid for up to 12 days (103 healthy study participants and 20 study participants). In EP0069, 55 study participants were exposed to repeated doses of PSL up to 400mg bid during the maintenance phase of the study. A total of 42 of the 55 study participants in EP0069 have enrolled in EP0073, during which they are allowed to adjust their PSL dose.

The safety findings to date suggest that the adverse events (AEs) experienced by study participants receiving single and repeated doses of PSL are limited principally to central nervous system (CNS) effects and that these are consistent with the known pharmacology of PSL, ie, similar to AEs produced by SV2A- and $GABA_A$-targeting AEDs. The AEs tend to be dose-related in frequency and intensity, self-limiting, and tend to decrease in intensity over the first few days of dosing.

The psychiatric findings currently reported across the Phase 1 and Phase 2 studies with PSL are consistent with the AE profile of other AEDs, including other SV2A ligands. Acute psychiatric effects occurred in 3 study participants administered PSL (2 in Phase 1 and 1 in Phase 2). The events were transient, acute, and required admission to psychiatric care and antipsychotics. No definite dose relationship could be determined, and the events occurred after variable periods of time after the first administration of PSL. The occurrence of these behavioral AEs highlights the need to consider the possibility of significant psychiatric AEs and to maintain vigilance for them.

With regard to cardiovascular effects, minor, transient, reductions in blood pressure (BP) were observed in the Phase 1 and Phase 2 PSL studies; however, these were not clinically meaningful and resolved without intervention. The degrees of reduction seen in both systolic and diastolic BP are consistent with the $GABA_A$-targeted mechanism of action of PSL and do not appear likely to have a clinically significant effect in therapeutic use (Jones et al, 1979). In regard to electrocardiogram (ECG) results, all nonclinical and clinical Phase 1 and Phase 2 cardiac data in totality were reviewed by an expert cardiologist consultant whose opinion was that “overall, there is no clear evidence that PSL is associated with any increase in incidence of ectopy, change in QT interval corrected for heart rate changes (QTc), or clinically-significant arrhythmia in clinical trials to date”. Echocardiographic screening of study participants at Baseline (to exclude study participants with valvulopathies) and ongoing echocardiographic monitoring during treatment and posttreatment has been implemented in the Phase 2 studies. No major findings were observed in the completed EP0069 study or the ongoing open-label extension study, EP0073. Cardiac monitoring (eg, ECGs, vital signs, echocardiograms) is planned throughout the duration of the PSL development program in order to better understand and mitigate any risks.

In general, the safety profile of PSL has been consistent with the pharmacological properties of the drug and with dose-escalation studies of CNS compounds in regards to the type and severity of nervous system and psychiatric AEs reported, with most AEs reported as mild or moderate.

The overall safety profile during the clinical program to date, as well as preclinical and clinical experience with PSL, can be found in the Investigator's Brochure (IB).

2.3 Risk assessment

Padsevonil is mainly metabolized via CYP3A4. Safety pharmacology studies have shown no major adverse effects on the respiratory and central nervous systems when administered orally in single-dose safety pharmacology studies (rats) and in repeat dose toxicity studies (rats, dogs). A slight prolongation of QTc was found in a 4-week study in dogs at 30mg/kg bid; however, it was not confirmed in a 13-week study (animals monitored by external telemetry) or a 39-week study at doses up to 50mg/kg bid, with free plasma concentration far above those reached in healthy study participants. Small, transient increases in heart rate and changes in arterial pressure (hypertension in rats and hypotension in dogs) occurring mainly from single doses are likely related to exaggerated $GABA_A$ pharmacologic activity.

In the 39-week dog toxicity study, subtle cardiac microscopic findings, consisting of minimal valvular inflammatory cell infiltration, or minimal to slight epithelial inflammation/fibroplasia of the epicardium in the right atrium, were seen in the heart of one-third of treated dogs without dose relationship. These findings were not seen in the 13-week study. Findings were subtle, focal, and not associated with any clinically significant cardiovascular changes. These findings did not cause any biological or clinical consequences in the animals in this study and were thus not considered to be adverse. This conclusion was supported after comprehensive review of the data by 5 nonclinical pathologists (including a cardiovascular expert pathologist). Additionally, external advice on the potential human implications was sought from a British Heart Foundation Professor of Cardiology. It was concluded that short-term exposure should not lead to any relevant abnormality or clinical disease, and even with long-term exposure the potential hazard and likelihood of an adverse pericardial or valvular effect in humans is extremely low.

Padsevonil is neither teratogenic nor embryotoxic in rats and rabbits. There was no effect on reproductive organs, including sperm analysis, following long-term administration (up to 26 weeks in rats and 39 weeks in dogs).

The preclinical pharmacology studies indicated that the metabolism of PSL may be affected by extrinsic influences on the CYP3A4/CYP2C19 pathway. In order to mitigate any risk caused by these interactions, medication or dietary ingredients that induce, inhibit, or are a substrate for the CYP3A4/CYP2C19 pathways are restricted. Further details are provided in Section 7.8.2 and Section 7.8.3, respectively.

In clinical trials, PSL had a good safety profile. There were no deaths. Adverse events experienced by study participants receiving single and repeated doses of PSL were limited principally to CNS effects and that these were consistent with its known pharmacology. Adverse events were dose-related in frequency and intensity, self-limiting, and tended to decrease in intensity over the first few days of dosing. Some new AEs (mainly headache and sleep disturbance) developed after dose discontinuation with PSL in the Phase 1 studies, indicating a potential withdrawal syndrome. These have been mild, transient, not dose-related and not of clinical concern.

The occurrence of acute psychiatric serious adverse events (SAEs) (delirious syndrome, mania-like symptoms, and acute psychosis) in 3 study participants administered PSL highlights the need to maintain vigilance for such events. Reported acute psychiatric effects are consistent with adverse effects of other anticonvulsant drugs with various mechanisms of action. These SAEs were transient, acute, and required clinical intervention (admission to psychiatric care and antipsychotics). In healthy study participants, those SAEs occurred early after initiation of PSL done without titration; in 1 study participant, symptoms worsened upon abrupt drug discontinuation. Only in 1 out of 68 epileptic study participants exposed to PSL, a psychotic effect emerged a few weeks following dosing start after improvement in seizure control. This suggests a "forced normalization" phenomenon, which is described with other AEDs in resistant patients and is not unexpected with a potent AED (Loganathan et al, 2015; Clemens, 2005). The mitigation plan for acute psychiatric effects involves gradual titration and taper, known to improve tolerability of AEDs.

Despite the occurrence of ECG findings such as ectopies (asymptomatic, not requiring clinical intervention), there are no current data suggesting that PSL has an adverse effect on cardiovascular function other than a minimal lowering effect on BP. The degrees of reduction of both supine blood pressure (SBP) and diastolic blood pressure (DBP) are consistent with the $GABA_A$-targeted mechanism of action of PSL and do not appear likely to have a clinically significant effect in therapeutic use. As a precaution from preclinical and clinical findings of non-clinically significant ECG abnormalities and hypotension, ECGs and vitals are being assessed frequently in current clinical studies.

There is no benefit for healthy study participants to participate in this study. However, the information obtained from this study will inform decisions on safe and effective doses of PSL to be given to epileptic study participants in future studies. The Sponsor will immediately notify the Principal Investigator (PI) and regulatory agencies if any additional safety or toxicology information becomes available during the study.

2.4 Urgent safety measures

In accordance with UK Law (Medicines for Human Use [Clinical Trials] as amended: SI 1031 Part 4 Section 30), the Sponsor and Investigator may take appropriate urgent safety measures in order to protect the study participants of a clinical study against any immediate hazard to their health or safety. If such measures are taken, the Sponsor shall immediately (no later than 3 days from the date the measures are taken) give written notice of the measures taken and the circumstances giving rise to those measures to the licensing authority and the relevant ethics committee.

3 STUDY OBJECTIVES

3.1 Primary objective

The primary objective of this study is to evaluate and compare the PK of PSL in the presence and absence of erythromycin in healthy study participants.

3.2 Secondary objectives

The secondary objectives of this study are to:

- Assess the safety and tolerability of PSL in the presence and absence of erythromycin in healthy study participants
- Evaluate and compare the plasma PK of PSL metabolites, [redacted] in the presence and absence of erythromycin in healthy study participants
- Assess and compare the urine PK of PSL and its metabolites [redacted] and [redacted]) in the presence and absence of erythromycin in healthy study participants

3.3 Exploratory objectives

The exploratory objectives of this study are to:

- Estimate the inter- and intra-study participant variability in the plasma PK of PSL and its metabolites following administration of PSL in the presence and absence of erythromycin
- Evaluate and compare the venous blood and MITRA microsampling (dried blood) PK of PSL and its metabolite [redacted] following administration of PSL in the presence and absence of erythromycin
- Archive blood samples for genotyping of drug metabolizing enzymes and biomarkers

4 STUDY VARIABLES

4.1 Pharmacokinetic variables

4.1.1 Primary pharmacokinetic variables

The primary PK variables will comprise C_{max} and $AUC_{(0-12)}$ following a single dose and $C_{max,ss}$ and AUC_{τ} following multiple doses of PSL in plasma:

- C_{max}: maximum observed plasma concentration
- $AUC_{(0-12)}$: area under the plasma concentration-time curve from time zero to 12 hours
- $C_{max,ss}$: maximum observed steady-state plasma concentration
- AUC_{τ}: area under the curve over a dosing interval (12 hours)

4.1.2 Secondary pharmacokinetic variables

The secondary PK variables for PSL will comprise t_{max}, and C_{min} following single dose and t_{max}, $t_{½,ss}$, λ_z, C_{trough}, and CL/F_{ss} following multiple doses, $C_{max,}$ $AUC_{(0-12),}$ $C_{max,ss}$, and AUC_{τ} for PSL

metabolites [redacted], and the metabolite-to-parent ratios for $C_{max,}$ $AUC_{(0\text{-}12),}$ and AUC_{τ} in plasma:

- t_{max}: time of maximum concentration
- C_{min}: minimum observed plasma concentration
- $t_{½,ss}$: apparent terminal elimination half-life at steady-state
- λ_z: apparent elimination rate constant
- C_{trough}: predose observed plasma concentration
- CL/F_{ss}: apparent total clearance at steady-state

Additionally, the secondary PK variables for PSL and its metabolites [redacted] will comprise CL_r, A_e, f_e, and CL_{form} in urine following a single dose and multiple doses:

- CL_r: renal clearance of PSL and its metabolites [redacted]
- A_e: cumulative amount of PSL or metabolites excreted into the urine
- f_e: fraction of PSL or metabolites excreted into the urine
- CL_{form}: formation clearance of metabolites

4.1.3 Other pharmacokinetic variables

The following other PK variables will be assessed during the study:

- Inter- and intra-study participant coefficients of variation (variability) in PK parameters for PSL and its metabolites
- Pharmacokinetic parameter (and profile) data derived from venous blood with MITRA (dried blood) microsampling for PSL and its metabolite (only [redacted])

4.2 Safety variables

4.2.1 Secondary safety variables

The following secondary safety variables will be assessed during the study:

- Incidence of AEs and SAEs

4.2.2 Other safety variables

The following other safety variables will be assessed during the study:

- Changes in vital signs (pulse rate, BP, respiratory rate, and body temperature)
- Changes in safety laboratory data (hematology, clinical chemistry, and urinalysis)
- Changes in 12-lead ECG assessments
- Physical examination (including neurological examination) findings

5 STUDY DESIGN

5.1 Study description

This is a Phase 1, open-label, DDI study designed to evaluate the effect of erythromycin on the PK and safety of PSL and its metabolites in a single cohort of 28 healthy study participants. The study uses a fixed-sequence multiple-dose design per recommendation for best practice (Liu et al, 2016).

The study consists of 5 periods: a Screening Period, 3 Treatment Periods, and a SFU Period (see Figure 5–1 for a schematic diagram).

5.2 Study periods

5.2.1 Screening Period

The Screening Period consists of a single Screening Visit, which will be conducted at the unit within 28 days prior to check-in for Treatment Period 1, and a Baseline Visit, which will be conducted at the unit 1 day prior to Treatment Period 1.

5.2.1.1 Screening Visit (Day -28 to Day -2)

Study participants are required to sign a written Informed Consent form (ICF) prior to the conduct of any study-related procedure. Screening assessments will be conducted, after which the eligibility of study participants will be determined based on: inclusion and exclusion criteria (see Section 6.1 and Section 6.2, respectively); demographics (including weight and height); medical history; full physical examination; medication history; vital sign measurements; several laboratory tests (hematology, serum chemistry, urinalysis, serology screening, alcohol breath test, cotinine test, and urine toxicology screen); triplicate 12-lead ECGs; and recording of AEs/medical procedures. A serum pregnancy test will be performed to assess eligibility for women of childbearing potential.

Study participants will also be assessed with the Columbia-Suicide Severity Rating Scale (C-SSRS) to assess suicidal risk.

5.2.1.2 Baseline Visit (Day -2 to Day -1)

At the Baseline Visit, study participants will check-in at the unit on Day -2 and receive a study participant Identification Card.

The following procedures/assessments will be repeated on Day -2: inclusion/exclusion criteria verification; demographics; medical history; C-SSRS; full physical examination; medication history; vital sign measurements; laboratory tests (hematology, chemistry profile, urinalysis, alcohol breath test, cotinine test, and urine toxicology screen); triplicate 12-lead ECGs; and recording of AEs/medical procedures. For women of childbearing potential, a serum pregnancy test will be performed.

Study participants will undergo the triplicate 12-lead ECG run-in on Day -1.

5.2.2 Treatment Periods

The study consists of a total of 3 Treatment Periods consisting of administration of PSL and/or erythromycin; Treatment Period 1 and Treatment Period 2 will be followed by a wash-out. For each Treatment Period, study participants will check into the unit 2 days prior to the first dosing

of PSL or erythromycin (Day -2, Day 10, and Day 21 for Treatment Period 1, Treatment Period 2, and Treatment Period 3b, respectively). Study participants will be discharged from the unit after the last urine sample for PK analysis is collected for each Treatment Period.

The full list of assessments to be performed at each visit is presented in Table 5-1.

During each check-in at the unit 2 days prior to PSL administration, the following procedures/assessments will be conducted: C-SSRS; a full physical examination; vital sign measurements; laboratory tests (chemistry, hematology, urinalysis, and alcohol breath, cotinine, and urine drug tests), and triplicate 12-lead ECGs.

For women of childbearing potential, a serum pregnancy test will be administered on Day 21 in Treatment Period 3a.

Administration of PSL 100mg bid during each treatment period will occur once in the morning, between 7AM and 10AM, and once in the evening, after the 12h postdose blood sample has been collected. Every effort should be made to ensure each study participant is dosed at the same times during the entire study. On each day of treatment, each dose will be given 30min after completion of a meal (see Section 7.8.3 for more details).

Adverse events will be recorded throughout the study. The Investigator will ensure that provisions are made for the study participants to contact the study site in case of AEs during the wash-out for Treatment Period 1 and Treatment Period 2. Such reporting of AEs and the Investigator's response will be accurately documented, and the UCB Study Physician will be notified immediately. The Investigator will also ensure clear instructions are provided on prohibited concomitant foods and medications (see Section 7.8.2).

5.2.2.1 Treatment Period 1 and Treatment Period 2 (Day 1 to Day 11 and Day 12 to Day 22)

Treatment Period 1 and Treatment Period 2 each consist of 5 days of treatment, followed by 1 week of wash-out.

During Treatment Period 1 and Treatment Period 2, study participants will receive PSL 100mg bid for 4 days (Day 1 to Day 4 and Day 12 to Day 15). On the fifth day (Day 5 and Day 16), 100mg of PSL will be given as a single dose in the morning. Study participants then enter 1 week of wash-out (from the evening of Day 5 to Day 11 and evening of Day 16 to Day 22).

Predose and postdose blood (venous and MITRA) and urine samples will be collected for PK analysis throughout the study (more details are provided in Section 5.3).

On Day 7 and Day 18, during the wash-out period, study participants will be discharged at the Investigator's discretion. Study participants may continue being confined to the unit at the Investigator's discretion. Study participants will check back into the unit on Day 10 and Day 21. Study participants will undergo the triplicate 12-lead ECG run-in on Day 11 and Day 22.

Study participants will be asked about the occurrence of AEs at check- in on Day 10, and via telephone contact on Day 20.

5.2.2.2 Treatment Period 3 (Day 23 to Day 38)

Treatment Period 3 consists of 2 erythromycin only periods (Treatment Period 3a and Treatment Period 3c) and a combined PSL/erythromycin treatment period (Treatment Period 3b). Study

participants will receive erythromycin at the same time PSL was administered in Treatment Period 1 and Treatment Period 2; erythromycin and PSL will be administered concurrently in Treatment Period 3b (see Section 5.2.2).

5.2.2.2.1 Treatment Period 3a (Day 23 to Day 25)

Study participants will receive erythromycin 500mg bid administered in the morning and in the evening.

5.2.2.2.2 Treatment Period 3b (Day 26 to Day 33)

Study participants will remain confined to the unit throughout Treatment Period 3b. Coadministration of PSL (100mg bid) and erythromycin (500mg bid) will begin on Day 26. Combination therapy will last for 8 days (Day 26 to Day 33). On Day 33, study participants will only receive a single dose of PSL 100mg in the morning, in addition to erythromycin 500mg bid.

Predose and postdose blood (venous and MITRA) and urine samples will be collected for PK analysis throughout the coadministration period (ie, Treatment Period 3b; see Section 5.3 for more details).

5.2.2.2.3 Treatment Period 3c (Day 34 to Day 38)

Study participants remain confined to the unit at the beginning of Treatment Period 3c. Study participants will receive erythromycin 500mg bid for the next 4 days (Day 34 to Day 37).

Study participants will be discharged on Day 38 at the Investigator's discretion if no serious safety issues occur.

5.2.3 Safety Follow-Up Period

The SFU Period consists of an End of Study (EOS) Visit performed 7 to 10 days after the final dose of erythromycin (Day 44 to Day 47) or upon discontinuation of the study. Study participants will have the following assessments completed at the EOS Visit: C-SSRS; a full physical examination; medication history; vital sign measurements; laboratory safety (hematology, chemistry, and urinalysis); triplicate 12-lead ECGs; and recording of AEs/medical procedures. A serum pregnancy test will also be administered for woman of childbearing potential.

5.3 Pharmacokinetic sampling

Full details regarding the collection of venous blood, microsamples of capillary blood, and urine, as well as samples to evaluate erythromycin levels and explore biomarkers, will be available in the Laboratory Manual.

5.3.1 Venous blood

Venous blood samples for PK analysis will be performed as follows:

- Predose and 0.25h, 0.5h, 0.75h, 1h, 1.25h, 1.5h, 2h, 3h, 4h, 6h, 8h, and 12h post first dose of PSL during each Treatment Period (Day 1, Day 12, and Day 26)
- Predose and 0.25h, 0.5h, 0.75h, 1h, 1.25h, 1.5h, 2h, 3h, 4h, 6h, 8h, 12h, 24h, 36h, 48h, and 72h post last dose of PSL during Treatment Period 1 (Day 5) and Treatment Period 2 (Day 16)

- Predose and 0.25h, 0.5h, 0.75h, 1h, 1.25h, 1.5h, 2h, 3h, 4h, 6h, 8h, 12h, 24h, 36h, 48h, 60h, 72h, 96h, and 120h post last dose of PSL during Treatment Period 3b (on the morning of Day 33)

Additional PK trough samples will be taken immediately prior to each morning dose of PSL during Treatment Period 1 (Day 2 through Day 4) and Treatment Period 2 (Day 13 through Day 15) and each morning combination dose during Treatment Period 3b (Day 27 through Day 33).

5.3.2 Microsamples of capillary blood

Samples from a finger skin prick will also be collected using the MITRA device at each of the time points identified for the venous blood samples in Section 5.3.1.

5.3.3 Urine

Urine samples for PK analysis will be collected as follows:

- Within 1h predose and 0h to 12h post first dose of PSL during each Treatment Period (Day 1, Day 12, and Day 26)
- 0h to 12h, 12h to 24h, and 24h to 48h post last PSL dose during Treatment Period 1 (Day 5) and Treatment Period 2 (Day 16)
- 0h to 12h, 12h to 24h, 24h to 48h, 48h to 72h, and 72h to 96h post last dose of PSL during Treatment Period 3b (Day 33)

Urine aliquots will be taken and stored from timed urine collections described above and in Table 5-1. Each collection period will be completed with a full urine void. Additionally, each study participant will be required to void prior to the IMP dose and an aliquot will be taken as baseline. Full details of urine collection will be available in the Laboratory Manual.

5.4 Study duration per study participant

The total duration of study per study participant will be approximately 75 days with a maximum of 18 days exposure to PSL.

The end of the study is defined as the date of the last visit of the last study participant in the study.

5.5 Planned number of study participants and sites

A total of 28 study participants are planned to be enrolled at 1 site.

5.6 Anticipated region and country

This study will be conducted in the United Kingdom.

5.7 Schedule of study assessments

The schedule of assessments is presented in Table 5-1.

Table 5-1: Schedule of assessments

Assessments/ procedures	Screening Period		Treatment Period											SFU Period
	Screen.	BL	1 and 2					3a	3b				3c	EOS
	Days		Days					Days						Day
	-28 to -2	-2 to -1 [a]	1 [b]	2-3	4	5	6-11	23-25	26	27-31	32	33	34-38	44, 45, 46, or 47 [c]
			12	13-14	15	16	17-22							
Written Informed Consent	X													
Inclusion/exclusion criteria verification	X	X												
Demographics, habits, and lifestyle	X	X												
General medical/psychiatric/ procedures history	X	X												
Study participant identification card assigned		X												
Admit to unit [d]		X					X	X						
Discharge from unit [e]							X						X	
C-SSRS [f]	X	X					X	X	X	X	X	X	X	X
Full physical examination [g]	X	X					X						X	X
Abbreviated physical examination [h]			X			X		X	X	X	X	X	X	
Prior and concomitant medications [i]	X	X	X											

Table 5-1: Schedule of assessments

Assessments/ procedures	Screening Period		Treatment Period											SFU Period
	Screen.	BL	1 and 2					3a	3b				3c	EOS
	Days		Days					Days						Day
	-28 to -2	-2 to -1 [a]	1 [b]	2-3	4	5	6-11	23-25	26	27-31	32	33	34-38	44, 45, 46, or 47 [c]
			12	13-14	15	16	17-22							
Vital signs [j]	X	X	X	X	X	X	X	X	X	X	X	X	X	X
Serum pregnancy test [k]	X	X					X						X	X
Telephone contact							X [l]							
Hematology, serum chemistry, urinalysis [m]	X	X			X		X		X	X		X	X	X
Serology (HIV, Hep B, and Hep C)	X													
Sample collection for exploratory genotype or biomarker analysis [n]			X	X		X								
12-lead ECG [o]	X	X	X	X	X	X	X	X	X	X	X	X	X	X
Urine and cotinine drug screen, alcohol breath test [k]	X	X					X							
Recording of AEs/medical procedures	X	X	X											

Table 5-1: Schedule of assessments

Assessments/ procedures		Screening Period		Treatment Period											SFU Period
		Screen.	BL	1 and 2					3a	3b				3c	EOS
		Days		Days					Days						Day
		-28 to -2	-2 to -1 [a]	1 [b]	2-3	4	5	6-11	23-25	26	27-31	32	33	34-38	44, 45, 46, or 47 [c]
				12	13-14	15	16	17-22							
Administer PSL 100mg	am			X	X	X	X			X	X	X	X		
	pm			X	X	X				X	X	X			
Administer erythromycin 500mg	am								X	X	X	X	X	X [p]	
	pm								X	X	X	X	X	X [n]	
Study drug accountability				X											
Blood sampling for PSL and metabolites PK levels				X [q]						X [r]					
Urine collection for PSL and metabolites PK levels				X [s]						X [t]					
Final Disposition Determination															X [u]

[a] The BL is defined as the 2 day period (D-2 and D-1) before D1. Day -1 is defined as 1 day before D1.
[b] D1 is defined as the first day of IMP administration.
[c] The EOS Visit will occur 7 to 10 days after the final dose of IMP is administered. The same assessments performed at the EOS Visit will be performed for a Withdrawal Visit, if applicable.
[d] Study participants will be confined to the unit beginning in the afternoon 2 days before the first PSL or erythromycin administration of each treatment period (D-2, D10, and D21).
[e] Study participants will be discharged from the unit after the last urine sample collection during each treatment period (D7, D18, and D38), at the Investigator's discretion.

[f] The C-SSRS will be done at Screening, when study participants are admitted to the unit (D-2, D10, and D21), before study participants are discharged from the unit (D7, D18, and D38), throughout Treatment Period 3b (Day 26 to Day 33), on D34 and D37 of Treatment Period 3c, and at the EOS Visit.

[g] A full physical examination will be performed at Screening, when study participants are admitted to the unit (D-2, D10, and D21), when study participants are discharged from the unit (D7, D18, and D38), and at the EOS Visit. During each treatment period, the full physical examination will be performed prior to each morning dosing of PSL and/or erythromycin.

[h] An abbreviated physical examination will be performed prior to each first PSL administration (D1, D12, and D26) of each treatment period, on D5 of Treatment Period 1, on D16 of Treatment Period 2, and on D24 through D37 during Treatment Period 3.

[i] Prior and concomitant medications will be recorded prior to morning dosing.

[j] Vital signs (including systolic and diastolic BP, pulse rate, respiration rate, and oral temperature) will be performed at Screening, when study participants are admitted to the unit (D-2, D10, and D21), before each morning dose of PSL and/or erythromycin throughout each treatment period, on D38, and at EOS.

[k] In addition to the Screening Visit, a serum pregnancy test (for women of childbearing potential only) and drug screen will be administered when study participants are admitted to the unit (D-2, D10, and D21). Additional serum pregnancy tests (for women of childbearing potential only) will be administered on D37 and at the SFU Visit.

[l] A telephone contact to verify any AE or concomitant treatment will occur on D9 and D20.

[m] Laboratory safety (hematology, chemistry, and urinalysis) will be performed after a fasting period of at least 4h only at Screening. Laboratory safety (non-fasting) will be performed prior to admission to the unit during each treatment period (D-1, D10, and D21), and prior to morning dosing on D4 during Treatment Period 1, on D15 during Treatment Period 2, and on D26, D30, D33, and D37 during Treatment Period 3, and at EOS.

[n] Genotype sample collection for potential exploratory analysis to be collected at predose on D1. Biomarker sample collection for potential exploratory analysis to be collected at predose on D1 and D12 and at 48h postdose on D1 and D12 (i.e., D3 and D14), as well as at 2h postdose on D5 and D16.

[o] Triplicate 12-lead ECGs will be performed after a rest of at least 5 minutes at 2- to 3-minute intervals for each of the following time points: the Screening Visit; D-1; D11; D38; the EOS Visit; predose, 1h, 2h, 3h and 6h postdose for each morning dose of PSL and/or erythromycin during each treatment period; and 0.5h predose for each evening dose of PSL and/or erythromycin during each treatment period. In addition, one day prior to first dose of PSL or erythromycin in Treatment Periods 1, 2 and 3 (that is, on D-1, D10, D22 and D25), triplicate 12-lead ECGs will be performed after a rest of at least 5 minutes at 2- to 3-minute intervals for each of the following matching time points: predose, 1h, 2h, 3h and 6h postdose for the morning administration of PSL and/or erythromycin, and 0.5h predose for the evening administration of PSL and/or erythromycin, where dosing time is equivalent to the expected time of dosing on the subsequent day (the triplicate 12-lead ECG run-in day).

[p] Erythromycin will not be administered on D38.

[q] Blood samples (venous and MITRA) for PK analysis will be collected relative to the morning dose as follows: predose and 0.25h, 0.5h, 0.75h, 1h, 1.25h, 1.5h, 2h, 3h, 4h, 6h, 8h, and 12h postdose on D1 and D12; and predose and 0.25h, 0.5h, 0.75h, 1h, 1.25h, 1.5h, 2h, 3h, 4h, 6h, 8h, 12h, 24h, 36h, 48h, and 72h post last morning dose of PSL on D5 and D16. Additional PK trough samples will be taken immediately prior to each morning dose on D2 to D4 (Treatment Period 1) and D13 to D15 (Treatment Period 2).

[r] Blood samples (venous and MITRA) for PK analysis will be collected relative to the morning dose as follows: predose and 0.25h, 0.5h, 0.75h, 1h, 1.25h, 1.5h, 2h, 3h, 4h, 6h, 8h, and 12h postdose on D26; and predose and 0.25h, 0.5h, 0.75h, 1h, 1.25h, 1.5h, 2h, 3h, 4h, 6h, 8h, 12h, 24h, 36h, 48h, 60h, 72h, 96h, and 120h post last dose of PSL on D33. Additional PK trough samples will be taken immediately prior to each morning dose on D27 to D33 (Treatment Period 3b).

[s] Urine collection for PK analysis will be collected relative to the morning dose as follows: ≤1h predose and 0h to 12h post first dose on D1 and D12; and 0h to 12h, 12h to 24h, and 24h to 48h post last PSL morning dose on D5 and D16.

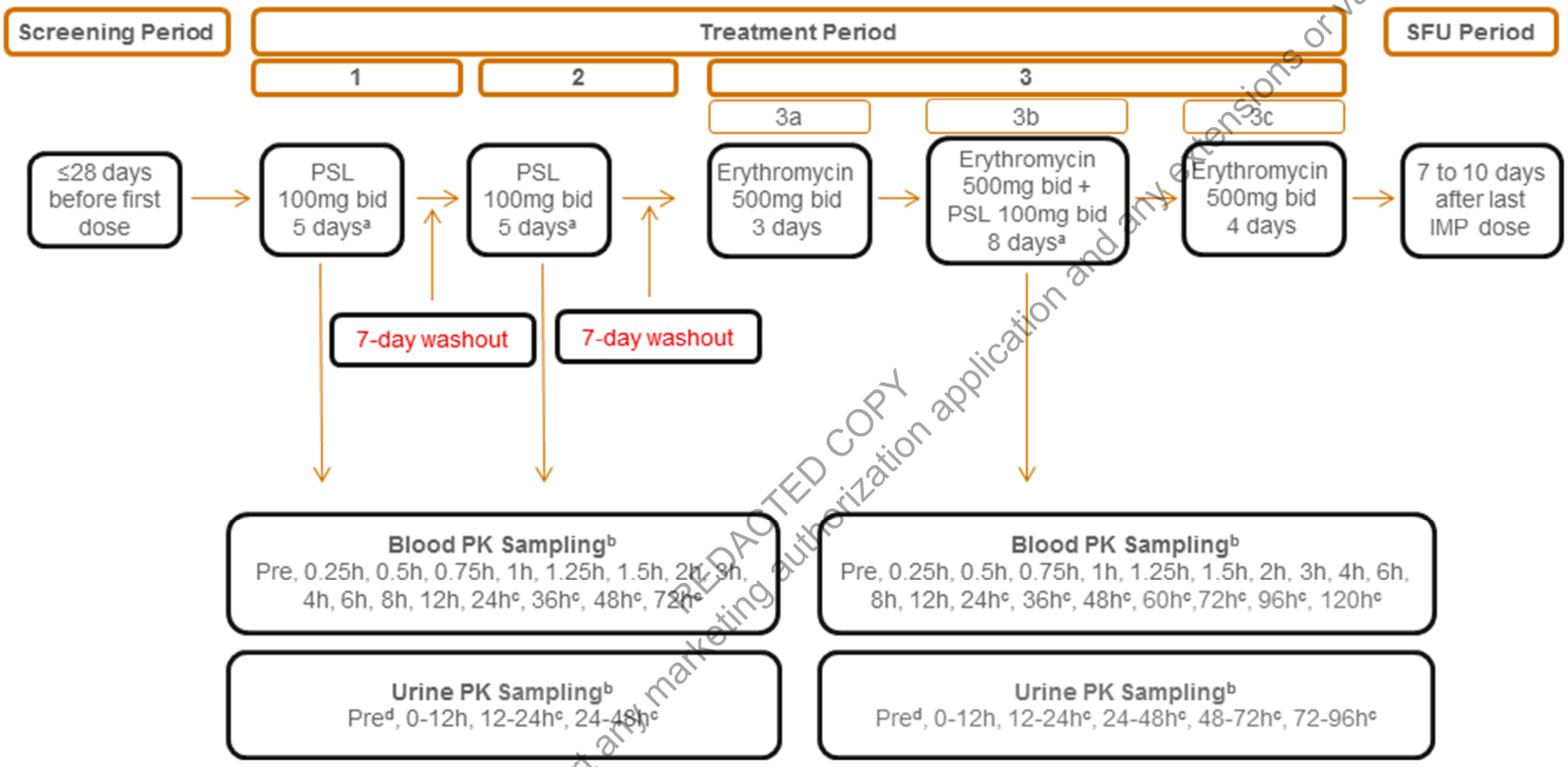
[t] Urine collection for PK analysis will be collected relative to the morning dose as follows: ≤1h predose and 0h to 12h post first dose on D26; and 0h to 12h, 12h to 24h, 24h to 48h, 48h to 72h, and 72h to 96h post last dose of PSL on D33.

[u] For study participants prematurely terminating or completing the study, final disposition is 7 to 10 days from final IMP dose (EOS). All study participants prematurely terminating from the study should be encouraged to undergo final evaluation procedures, in accordance with the EOS schedule, as soon as possible after the final dose of IMP.

5.8 Schematic diagram

The study schematic diagram for UP0057 is presented in Figure 5–1.

Figure 5–1: Schematic diagram



bid=twice daily; IMP=investigational medicinal product; PK=pharmacokinetic(s); PSL=padsevonil; SFU=Safety Follow-Up
[a] On the last day of Treatment Period 1, Treatment Period 2, and Treatment Period 3b, PSL will only be administered once in the morning.
[b] First and last PSL dose.
[c] Only after last PSL dose.
[d] Only after first PSL dose.

5.9 Rationale for study design and selection of dose

Padsevonil is being administered at a dose of 100mg bid to evaluate and compare the plasma and urine PK, as well as the safety and tolerability profile, of PSL in the presence and absence of erythromycin. The plasma and urine PK of the known metabolites of PSL will also be evaluated and compared in the presence and absence of erythromycin. This dose has been selected to ensure that safety margins are not exceeded following administration of PSL with a CYP3A4 inhibitor and that the effect of CYP2C19 auto-inhibition on PSL metabolism is achieved in addition to the overall effect of CYP3A4 inhibition. In addition, 100mg is 1 of the doses planned to be investigated in the dose-ranging study, EP0091. Erythromycin given at a dose of 500mg bid is expected to increase exposure to PSL by approximately 3.7-fold (SimCYP simulations).

6 SELECTION AND WITHDRAWAL OF STUDY PARTICIPANTS

6.1 Inclusion criteria

To be eligible to participate in this study, all of the following criteria must be met:

1. Study participant is informed and given ample time and opportunity to think about his/her participation and has signed and dated the written ICF approved by an Independent Ethics Committee (IEC).
2. Study participant is considered reliable and capable of adhering to the protocol and visit schedule according to the judgment of the investigator.
3. Study participant is male or female and between 18 and 55 years of age (inclusive).
4. Study participant is of a body weight of at least 50kg for males and 45kg for females, as determined by a body mass index (BMI) between 18 and 30kg/m2.
5. Study participant is in good physical and mental health as determined on the basis of the medical history and general physical examination (ie, study participant has no current or past medical history of clinical significance).
6. Female study participants use an efficient form of contraception for the duration of the study (unless menopausal [defined as no menses for 12 months without an alternative medical cause]; a high follicle-stimulating hormone level in the postmenopausal range may be used to confirm a postmenopausal state in women not using hormonal contraception or hormonal replacement therapy). Hormonal contraception may be susceptible to an interaction with the IMP, which may reduce the efficacy of the contraception method. The potential for reduced efficacy of any hormonal contraception methods requires that a barrier method (preferably male condom) also be used.

   Birth control methods considered as an efficient form of contraception:

   – Combined (oestrogen and progestogen containing) hormonal contraception (oral, implant, or injectable) associated with inhibition of ovulation in combination with a barrier method (preferably male condom)

   – Progestogen-only hormonal contraception associated with inhibition of ovulation in combination with a barrier method (preferably male condom)

- Intrauterine device (IUD)
- Intrauterine hormone-releasing system (IUS) in combination with a barrier method (preferably male condom)
- Bilateral tubal occlusion
- Vasectomized partner
- Sexual abstinence

  True abstinence is an acceptable form of contraception when this is in line with the preferred and usual lifestyle of the person. Periodic abstinence (eg, calendar ovulation, symptothermal, postovulation methods), declaration of abstinence for the duration of the study, and withdrawal are not acceptable methods of contraception.
- Progestogen-only oral hormonal contraception, where inhibition of ovulation is not the primary mode of action in combination with a barrier method (preferably male condom)
- Male or female condom with spermicide (ie, double barrier)
- Cap, diaphragm, or sponge with spermicide

  To ensure proper birth control, females who use hormonal contraception should use an efficient barrier contraceptive in the 3 months following the end of the study (ie, for 3 months after the last intake of study medication).

7. Study participant has clinical laboratory test results within the local reference ranges or values are considered as not clinically relevant by the investigator and approved by the UCB Study Physician. Lab parameters outside the reference ranges can be retested and if the retest result is within the reference range or considered as clinically not relevant the study participant will be allowed in the study. Alanine aminotransferase (ALT), aspartate aminotransferase (AST), or alkaline phosphatase (ALP) should be within the normal limits. Liver enzymes up to 25% above the upper limit may be repeated once and should be within normal limits before inclusion.
8. Study participant has BP and pulse rate within normal range in supine position after 10 minutes of rest (SBP: 90 to 140mmHg, DBP: 40 to 90mmHg, pulse rate: 40 to 100bpm). In case of an out of range result, 1 repeat will be allowed. If out of range again, the study participant cannot be included.
9. Male study participant agrees that, during the study period, when having sexual intercourse with a woman of childbearing potential, he will use an efficient barrier contraceptive (condom plus spermicide) AND that the respective partner will use an additional efficient contraceptive method (eg, oral pills, IUDs, or diaphragm, and spermicide).

6.2 Exclusion criteria

Study participants are not permitted to enroll in the study if any of the following criteria is met:

1. Study participant has previously received IMP in this study.
2. Study participant has participated in another study of an IMP (or a medical device) within the previous 3 months before Screening (or within 5 half-lives for the IMP, whichever is longer) or is currently participating in another study of an IMP (or a medical device).
3. Study participant has a history of drug or alcohol dependency within the previous 6 months or tests positive for alcohol (breath test) and/or drugs of abuse (urine test) at the Screening Visit.
4. Study participant has a current or past psychiatric condition that, in the opinion of the Investigator, could compromise his/her safety or ability to participate in this study or a history of schizophrenia, or other psychotic disorder, bipolar disorder, or severe unipolar depression. The presence of potential psychiatric exclusion criteria will be determined based on the psychiatric history collected at Screening.
5. Study participant has a lifetime history of suicide attempt (including an [redacted]), or [redacted] as indicated by a positive response ("Yes") to either Question 4 or Question 5 of the "Screening/Baseline" version of the C-SSRS at Screening.
6. Study participant has any medical condition that, in the opinion of the Investigator, could jeopardize or would compromise the study participant's ability to participate in this study.
7. Study participant has a known hypersensitivity to any components of the IMP as stated in this protocol.
8. Study participant has made a blood or plasma donation or has had a comparable blood loss (>400mL) within the last 3 months prior to the Screening Visit.
9. Study participant has a consumption of more than 3 units of alcohol/day in case of females, more than 4 units of alcohol/day in case of males.
10. Study participant smokes more than 5 cigarettes per day (or equivalent) or has done so within 6 months prior to the Screening Visit.
11. Study participant has a consumption of more than 600mg of caffeine/day (200mL of coffee contains approximately 100mg of caffeine, 200mL of black tea approximately 30mg, and 200mL of cola approximately 20mg).
12. Study participant has a diet, which deviates notably from the "normal" amounts of protein, carbohydrate, and fat, as judged by the investigator (eg, vegetarians or vegans).
13. Study participant is taking any concomitant medication currently or within 2 weeks prior to the first day of dosing with the exception of paracetamol (acetaminophen) which is allowed to be taken orally up to 1000mg per dose (up to 2000mg per day).
14. Study participant has received any prescription or nonprescription medicines, including enzyme inhibitors or inducers, over-the-counter (OTC) remedies, herbal and dietary supplements (including St. John's Wort), vitamins up to 2 weeks or 5 half-lives of the

respective drug (whichever is longer) before the first administration of IMP and during the clinical part of the study, unless required to treat an AE. This does not include oral contraceptives not exceeding 30µg ethinyl estradiol or postmenopausal hormone replacement therapy or implants, patches, or IUDs/IUSs delivering progesterone (for female study participants).

15. Study participant tests positive for human immunodeficiency virus 1/2 antibodies (HIV-1/2-Ab), hepatitis B surface antigen (HBsAg), or hepatitis C virus antibody (HCV-Ab).
16. Study participant has > upper limit of normal (ULN) of any of the following: ALT, AST, ALP, or total bilirubin (≥1.5xULN total bilirubin if known Gilbert's syndrome). If study participant has elevations only in total bilirubin that are >ULN and <1.5xULN, fractionate bilirubin to identify possible undiagnosed Gilbert's syndrome (ie, direct bilirubin <35%). To be enrolled, study participants must have ALT, AST, or ALP values within the ULN.
17. Tests that result in ALT, AST, or ALP up to 25% above the exclusion limit may be repeated once for confirmation. If out of range again, the study participant cannot be included.
18. Study participant has clinically relevant out-of-range values for hematology, and clinical chemistry, or urinalysis variables at the Screening Visit.
19. Study participant has any clinically significant abnormal physical examination and vital signs at the Screening Visit or confinement.
20. Study participant has any clinically relevant ECG finding at the Screening Visit or confinement. Study participant has an abnormality in the 12-lead ECG that, in the opinion of the investigator, increases the risks associated with participating in the study. In addition, any study participant with any of the following findings will be excluded: (a) QT interval corrected for heart rate using Bazett's formula (QTcB) or Fridericia's formula (QTcF) >450ms in 2 of 3 ECG recordings; (b) other conduction abnormalities (defined as PR interval ≥220ms); (c) irregular rhythms other than sinus arrhythmia or occasional, rare supraventricular or rare ventricular ectopic beats. In case of an out of range result, 1 repeat will be allowed. If out of range again, the study participant cannot be included.
21. Study participant performs heavy physical exertion less than 3 days before confinement.
22. Study participant has a history within the last 5 years or present condition of malignancy, with the exception of basal cell carcinoma.
23. Study participant ingests grapefruit (as beverage, fruit, or supplements) within 72 hours before each administration of IMP. If this is the case at the start of the study, study participants may be rescreened.
24. Female study participant tests positive for pregnancy, plans to get pregnant during the participation in the study, or who is breastfeeding.

6.3 Withdrawal criteria

Study participants are free to withdraw from the study at any time, without prejudice to their continued care.

Study participants must be withdrawn from the study if any of the following events occur:

1. Study participant develops a clinically relevant medical condition (or laboratory parameter) that, in the opinion of the Investigator, jeopardizes or compromises the study participant's ability to participate in this study or makes it unsafe to continue (for example a psychiatric event).
2. Study participant withdraws his/her consent.
3. The Sponsor or a regulatory agency requests withdrawal of the study participant.
4. An ECG shows an absolute QTcF value >500ms or >60ms prolongation above Baseline (defined as the mean of triplicate ECG taken at predose on Day 1, Day 12, Day 23 or Day 26) in 1 or more ECG recordings.
5. Study participant develops second- or third-degree atrioventricular block or another clinically relevant change in ECG results as determined by the Investigator.
6. Refer to Section 6.4.1 for withdrawal criteria in relation to potential drug-induced liver injury (PDILI).
7. Study participant tests positive for pregnancy at any point during the study.

Study participants may be withdrawn from the study if any of the following events occur:

8. Study participant is noncompliant with the study procedures or IMP in the opinion of the Investigator.
9. Study participant takes prohibited concomitant medications as defined in this protocol.

If the withdrawal occurs following dosing with IMP, the study participant will be asked to return for the EOS Visit 7 to 10 days after last intake of IMP.

The Investigator should attempt to obtain information on study participants in the case of withdrawal or discontinuation. For study participants considered as lost to follow up, the Investigator should make an effort (at least 1 phone call and 1 written message to the study participant), and document his/her effort (date and summary of the phone call and copy of the written message in the source documents), to complete the final evaluation. All results of these evaluations and observations, together with a narrative description of the reason(s) for removing the study participant, must be recorded in the source documents. The electronic Case Report form (eCRF) must document the primary reason for withdrawal or discontinuation.

Investigators should contact the Sponsor Study Physician, whenever possible, to discuss the withdrawal of a study participant in advance.

6.4 Stopping rules

Dosing should be stopped in case of:

- A serious adverse reaction (AR) (ie, an SAE considered at least possibly related to the IMP administration) in 1 study participant
- Any severe nonserious AR (ie, severe nonserious AEs considered as, at least, possibly related to the IMP administration) in 2 study participants

In the event that the stopping criteria are reached, the Investigator will ensure all necessary actions at the site are taken to prevent further administration of IMP to any study participant. Subsequently an internal UCB safety review meeting (Safety Monitoring Committee) will be organized.

If, following the internal safety review, it is appropriate to continue the study with or without dose adaptations, potential additional safety assessments, or changes in design, a substantial amendment will be submitted to the Medicines and Healthcare products Regulatory Agency (MHRA) and Research Ethics Committee (REC). The study will not restart until the amendment has been approved by the MHRA and REC.

6.4.1 Potential drug-induced liver injury investigational medicinal product discontinuation criteria

Study participants with PDILI must be assessed to determine if IMP must be discontinued. In addition, all concomitant medications and herbal supplements that are not medically necessary should also be discontinued.

The PDILI criterion below requires immediate and permanent discontinuation of IMP:

- Study participants with ≥3xULN ALT or AST

Evaluation of PDILI must be initiated as described in Section 10.2.1. If study participants are unable to comply with the applicable monitoring schedule, IMP must be discontinued immediately.

Investigators should attempt to obtain information on study participants in the case of IMP discontinuation to complete the final evaluation. Study participants with PDILI should not be withdrawn from the study until investigation and monitoring are complete. All results of these evaluations and observations, as well as the reason(s) for IMP discontinuation and study participant withdrawal (if applicable), must be recorded in the source documents. The eCRF must document the primary reason for IMP discontinuation.

7 STUDY TREATMENTS

7.1 Description of investigational medicinal products

Padsevonil (25mg tablets) will be supplied by UCB.

Erythromycin (500mg tablets) will be supplied by the study site.

7.2 Treatments to be administered

Padsevonil 100mg (as 4 tablets of 25mg) and/or erythromycin 500mg tablets will be administered orally with 8oz (240mL) water, 30min after a light or standard meal (more details are provided in Section 7.8.3).

Treatments will be administered in an open-label fashion. Study participants will be dosed in an upright position and should remain semi-recumbent until 4 hours afterwards.

7.3 Packaging

Padsevonil tablets are manufactured, packaged, and labeled according to Good Manufacturing Practice (GMP) guidelines and applicable laws or regulations.

7.4 Labeling

Clinical drug supplies will be labeled in accordance with the current International Council for Harmonisation (ICH) guidelines on Good Clinical Practice (GCP) and GMP and will include any locally required statements.

7.5 Handling and storage requirements

The Investigator (or designee) is responsible for the safe and proper storage of IMP at the site. Investigational medicinal product stored by the Investigator is to be kept in a secured area with limited access according to the storage conditions mentioned on the label.

Appropriate storage conditions must be ensured either by controlling the temperature (eg, room, refrigeration unit) or by completion of a temperature log in accordance with local requirements on a regular basis (eg, once a week), showing actual and minimum/maximum temperatures reached over the time interval.

In case an out-of-range temperature is noted, it must be immediately reported as per instructions contained in the IMP Handling Manual.

7.6 Drug accountability

A Drug Accountability form will be used to record IMP dispensing information on a by-study participant basis and will serve as source documentation during the course of the study. Details of any IMP lost, damaged (due to breakage or wastage), not used, partially used, or disposed of at the study site must also be recorded on the appropriate forms. All supplies and pharmacy documentation must be made available throughout the study for UCB (or designee) to review.

The Investigator (or designee) is responsible for retaining all used, unused, and partially used containers of IMP until destroyed.

The Investigator may assign some of the Investigator's duties for drug accountability at the study site to an appropriate pharmacist/designee.

The Investigator must ensure that the IMP is used only in accordance with the protocol.

Periodically, and/or after completion of the clinical period of the study, all used (including empty containers)/partially used, unused, damaged, and/or expired IMP must be reconciled and destroyed at the site according to local laws, regulations, and UCB Standard Operating Procedures (SOPs). Investigational medicinal product intended for the study cannot be used for any other purpose than that described in this protocol.

More information regarding IMP destruction is provided in the IMP Handling Manual.

7.7 Procedures for monitoring study participant compliance

Administration of PSL or erythromycin will be performed under the supervision of the Investigator (or designee), and the Investigator (or designee) will check the study participant's hands and the oral cavity immediately after dosing to confirm ingestion of the IMP. Compliance will be monitored by drug accountability and by drug assay (using the drug concentration in the blood). Compliance with the IMP is defined as consumption by the study participant that conforms 100% with the planned dosage.

Drug administration/consumption will be recorded and any discrepancies with the dosing regimen must be explained.

7.8 Concomitant medications/treatments

7.8.1 Permitted concomitant treatments (medications and therapies)

The use of concomitant medications during this study should be avoided, unless necessary to treat AEs or approved on a case by case basis prior to enrollment (eg, hormonal contraceptives) The use of any concomitant medications should be approved by the Sponsor in advance, in writing, when possible.

7.8.2 Prohibited concomitant treatments (medications and therapies)

With the exception of paracetamol up to 1000mg per dose (up to 2000mg per day), all prescription or nonprescription medicines are prohibited within 2 weeks prior to the first day of dosing. This includes enzyme inhibitors or inducers (eg, strong inhibitors or inducers of CYP3A4 or CYP2C19), OTC remedies, vitamins, and herbal and dietary supplements (including St. John's Wort) that are prohibited within 2 weeks or 5 half-lives of the respective drug (whichever is longer) before first administration of IMP and during the clinical part of the study, unless required to treat an AE. This does not include oral contraceptives not exceeding 30µg ethinyl estradiol or postmenopausal hormone replacement therapy or implants, patches, or IUDs/IUSs delivering progesterone (for female study participants). Drugs of unknown half-lives are prohibited within 2 weeks before administration of IMP and during the clinical part of the study, unless required to treat an AE.

If a study participant needs or takes any prohibited medication, the Investigator will (where possible) discuss with the Sponsor Study Physician and a decision will be made whether the study participant can continue in the study or must be withdrawn.

7.8.3 Diet, fluid, and activity control

During each treatment period, study participants will complete a light meal 30min prior to each morning dose of IMP, and a standard meal 30min prior to each evening dose of IMP. On the

ECG run-in days where study participants do not receive IMP (that is, Day -1, Day 11, and Day 22, see Section 10.3.3), study participants will receive a light meal in the morning and a standard meal in the afternoon and evening at approximately the same time as it is expected to be given on the subsequent dosing days.

Study participants should keep their usual diet (besides the restrictions for the study) necessary for the maintenance of good health; excessive food consumption should be avoided. Study participants should refrain from heavy physical exertion (eg, vigorous exercise) from 3 days prior to (first) confinement and during the study.

Study participants should not consume more than 3 units alcohol/day (females) and 4 units alcohol/day (males), or more than 600mg of caffeine/day (200mL of coffee contains approximately 100mg of caffeine, 200mL of black tea approximately 30mg, and 200mL of cola approximately 20mg) from 48 hours prior to each administration of PSL and until the final PK plasma sampling of each dosing period.

Grapefruit (as beverage, fruit, or supplements) within 72 hours before each administration of IMP will not be allowed. If this is the case at start of study, study participants may be rescreened.

Study participants must refrain from donating blood or plasma during the course of the study (except for the samples taken for the purpose of the study) and should refrain from donating blood or plasma for at least 3 months prior to the Screening Visit and until 2 months after the end of the study.

Water will be available ad libitum except for between 1 hour before and 2 hours after dosing. A total of 240mL of water will be given to each study participant at the time of administration of IMP.

7.9 Blinding

UP0057 is an open-label study; thus, there will be no blinding.

7.10 Numbering of study participants

Each study participant will receive a unique 5-digit number assigned at Screening that serves as the study participant identifier throughout the study. If the study participant withdraws or is withdrawn from the study, this number will not be reassigned to another study participant.

8 STUDY PROCEDURES BY VISIT

8.1 Screening Period (Day -28 to Day -1)

8.1.1 Screening Visit (Day -28 to Day -2)

The Screening Visit will be conducted at the unit within 28 days prior to check-in for Treatment Period 1. The following procedures/assessments will be performed:

- Written Informed Consent
- Inclusion/exclusion criteria verification
- Demographics, habits, and lifestyle
- General medical/psychiatric/procedures history

- C-SSRS (Baseline)
- Full physical examination
- Prior and concomitant medications
- Vital signs (including systolic and diastolic BP, pulse rate, respiration rate, and oral temperature)
- Blood and urine samples for the following clinical laboratory tests will be collected:
  - Serum pregnancy test (for women of childbearing potential only)
  - Hematology, serum chemistry, and urinalysis
  - Serology screening
  - Urine and cotinine drug screen
- Alcohol breath test
- Triplicate 12-lead ECGs
- Recording of AEs/medical procedures

8.1.2 Baseline Visit (Day -2 to Day -1)

Study participants will check into the unit 2 days prior to dosing and will be assigned their study participant identification card. The following procedures/assessments will be performed on Day -2:

- Inclusion/exclusion criteria verification
- Demographics, habits, and lifestyle
- General medical/psychiatric/procedures history
- C-SSRS
- Full physical examination
- Prior and concomitant medications
- Vital signs (including systolic and diastolic BP, pulse rate, respiration rate, and oral temperature)
- Blood and urine samples for the following clinical laboratory tests will be collected:
  - Serum pregnancy test (for women of childbearing potential only)
  - Hematology, serum chemistry, and urinalysis
  - Urine and cotinine drug screen
- Alcohol breath test
- Triplicate 12-lead ECGs
- Recording of AEs/medical procedures

The following procedures/assessments will be performed on Day -1:

- Triplicate 12-lead ECGs (run-in day):
  - Morning: Predose, 1h, 2h, 3h, and 6h postdose (where dosing time is equivalent to the expected time of dosing on the subsequent day)
  - Evening: approximately 0.5h predose (where dosing time is equivalent to the expected time of dosing on the subsequent day)

8.2 Treatment Period 1 (Day 1 to Day 5) and Treatment Period 2 (Day 12 to Day 16)

Study participants will check into the unit on Day -2 in Treatment Period 1 and Day 10 in Treatment Period 2, 2 days prior to the first dosing of PSL (Day 1 for Treatment Period 1 and Day 12 for Treatment Period 2).

All morning doses will be administered between 7AM and 10AM, 30min after completion of a light meal. When applicable, evening doses will be administered after the 12h postdose blood sample has been collected, 30min after completion of a standard meal. Every effort should be made to ensure each study participant is dosed at the same times during the entire study.

8.2.1 Day 1 (Treatment Period 1) and Day 12 (Treatment Period 2)

Study participants will receive PSL 100mg bid. The following procedures/assessments will be performed:

- Abbreviated physical examination prior to morning dosing
- Prior and concomitant medications recorded prior to morning dosing
- Vital signs (including systolic and diastolic BP, pulse rate, respiration rate, and oral temperature) prior to morning dosing
- Genotype (predose)
- Biomarker sample (predose)
- Blood samples (venous and MITRA) for PK analysis (relative to morning dosing)
  - Predose
  - Postdose: 0.25h, 0.5h, 0.75h, 1h, 1.25h, 1.5h, 2h, 3h, 4h, 6h, 8h, and 12h
- Urine samples for PK analysis (relative to morning dosing)
  - Predose (≤1h before dosing)
  - Postdose: 0 to 12h
- Triplicate 12-lead ECGs
  - Morning dose: Predose, 1h, 2h, 3h, and 6h postdose
  - Evening dose: approximately 0.5h predose
- Recording of AEs/medical procedures

8.2.2 Day 2 to Day 3 (Treatment Period 1) and Day 13 to Day 14 (Treatment Period 2)

Study participants will receive PSL 100mg bid. The following procedures/assessments will be performed:

- Prior and concomitant medications recorded prior to morning dosing
- Vital signs (including systolic and diastolic BP, pulse rate, respiration rate, and oral temperature) prior to morning dosing
- Biomarker sample on Day 3 and Day 14 (at 48h postdose Day 1)
- Blood samples for PK trough analysis will be collected immediately prior to morning dosing
- Triplicate 12-lead ECGs
  - Morning dose: Predose,1h, 2h, 3h, and 6h postdose
  - Evening dose: approximately 0.5h predose
- Recording of AEs/medical procedures

8.2.3 Day 4 (Treatment Period 1) and Day 15 (Treatment Period 2)

Study participants will receive PSL 100mg bid. The following procedures/assessments will be performed:

- Prior and concomitant medications recorded prior to morning dosing
- Vital signs (including systolic and diastolic BP, pulse rate, respiration rate, and oral temperature) prior to morning dosing
- Blood and urine samples for the following clinical laboratory tests will be collected prior to morning dosing:
  - Hematology, serum chemistry, and urinalysis
- Blood samples for PK trough analysis will be collected prior to morning dosing
- Triplicate 12-lead ECGs
  - Morning dose: Predose, 1h, 2h, 3h and 6h postdose
  - Evening dose: approximately 0.5h predose
- Recording of AEs/medical procedures

8.2.4 Day 5 (Treatment Period 1) and Day 16 (Treatment Period 2)

Study participants will receive PSL 100mg once in the morning. The following procedures/assessments will be performed:

- Abbreviated physical examination
- Prior and concomitant medications recorded prior to morning dosing

- Vital signs (including systolic and diastolic BP, pulse rate, respiration rate, and oral temperature) prior to morning dosing
- Biomarker sample: 2h postdose
- Blood samples (venous and MITRA) for PK analysis
  - Predose
  - Postdose: 0.25h, 0.5h, 0.75h, 1h, 1.25h, 1.5h, 2h, 3h, 4h, 6h, 8h, 12h, 24h, 36h, 48h, and 72h
- Urine samples for PK analysis
  - Postdose: 0 to 12h, 12h to 24h, and 24h to 48h
- Triplicate 12-lead ECGs
  - Morning dose: Predose, 1h, 2h, 3h, and 6h postdose
- Recording of AEs/medical procedures

8.3 Wash Out (Day 6 to Day 11 for Treatment Period 1; Day 17 to Day 22 for Treatment Period 2)

After the procedures and assessments are completed following the morning dose on Day 5, study participants enter a 1-week wash-out period.

Study participants will check-in to the unit on Day 10 and Day 21 and undergo the following procedures/assessments on Day 11 and Day 22:

- Triplicate 12-lead ECGs (run-in day):
  - Morning: Predose, 1h, 2h, 3h, and 6h postdose (where dosing time is equivalent to the expected time of dosing on the subsequent day)
  - Evening: approximately 0.5h predose (where dosing time is equivalent to the expected time of dosing on the subsequent day)

8.3.1 Day 6 (Treatment Period 1) and Day 17 (Treatment Period 2)

Study participants will remain at the unit and receive the following procedures/assessments:

- Prior and concomitant medications
- Blood samples (venous and MITRA) for PK analysis (24h and 36h after dosing on Day 5 and Day 16, see Section 8.2.4)
- Urine samples for PK analysis (24h to 48h after dosing on Day 5 and Day 16, see Section 8.2.4)
- Recording of AEs/medical procedures

8.3.2 Day 7 (Treatment Period 1) and Day 18 (Treatment Period 2)

After the following procedures and assessments, study participants will be discharged from the unit, provided there are no clinically significant safety issues that require extended supervision in the opinion of the PI:

- C-SSRS
- Full physical examination
- Prior and concomitant medications
- Blood samples (venous and MITRA) for PK analysis (48h after dosing on Day 5 and Day 16, see Section 8.2.4)
- Urine samples for PK analysis (24h to 48h after dosing on Day 5 and Day 16, see Section 8.2.4)
- Recording of AEs/medical procedures

8.3.3 Day 8 (Treatment Period 1) and Day 19 (Treatment Period 2)

Study participants will return to the unit for the following procedures/assessments:

- Prior and concomitant medications
- Blood (venous and MITRA) for PK analysis (72h after dosing on Day 5 and Day 16, see Section 8.2.4)
- Recording of AEs/medical procedures

8.3.4 Day 9 to Day 10 (Treatment Period 1) and Day 20 to Day 22 (Treatment Period 2)

Study participants will check back into the unit on Day 10 and Day 21. Study participants will be asked about the occurrence of AEs at check-in on Day 10, and via telephone contact on Day 20.

8.3.5 Day 10 (Treatment Period 1) and Day 21 (Treatment Period 2)

Study participants will check into the unit of Day 10 and Day 21, 2 days prior to receiving the first dose in Treatment Period 2 (on Day 12) and Treatment Period 3 (Day 23). The following procedures/assessments will be performed on Day 10 and Day 21:

- C-SSRS
- Full physical examination
- Prior and concomitant medications
- Vital signs (including systolic and diastolic BP, pulse rate, respiration rate, and oral temperature)
- Blood and urine samples for the following clinical laboratory tests will be collected:
  - Serum pregnancy test (for women of childbearing potential only)
  - Hematology, serum chemistry, and urinalysis

  - Urine and cotinine drug screen
- Alcohol breath test
- Triplicate 12-lead ECGs
- Recording of AEs/medical procedures

Study participants will undergo the triplicate 12-lead ECG run-in on Day 11 and Day 22 (see Section 8.3).

8.4 Treatment Period 3 (Day 23 to Day 37)

Study participants will check into the unit on Day 21, 2 days prior to receiving the first dose of erythromycin on Day 23 in Treatment Period 3. Study participants will undergo the triplicate 12-lead ECG run-in on Day 22 (see Section 8.3). Treatment Period 3 consists of 2 erythromycin only periods (Treatment Period 3a and Treatment Period 3c) and a combined PSL/erythromycin treatment period (Treatment Period 3b).

All morning doses will be administered between 7AM and 10AM, 30min after completion of a light meal. When applicable, evening doses will be administered after the 12h postdose blood sample has been collected, 30min after completion of a standard meal. Every effort should be made to ensure each study participant is dosed at the same times during the entire study.

8.4.1 Treatment Period 3a (Day 23 to Day 25)

Study participants will receive erythromycin 500mg bid administered in the morning and in the evening.

8.4.1.1 Day 23 to Day 25

The following procedures/assessments will be performed:

- Prior and concomitant medications recorded prior to morning dosing
- Abbreviated physical exam prior to morning dosing
- Vital signs (including systolic and diastolic BP, pulse rate, respiration rate, and oral temperature) prior to morning dosing
- Triplicate 12-lead ECGs
  - Morning dose: Predose, 1h, 2h, 3h and 6h postdose
  - Evening dose: approximately 0.5h predose
- Recording of AEs/medical procedures

8.4.2 Treatment Period 3b (Day 26 to Day 33)

Study participants will be confined to the unit for the duration of Treatment Period 3b. Padsevonil 100mg bid will be coadministered with erythromycin 500mg bid on Day 26 to Day 32 during Treatment Period 3b. On Day 33, PSL 100mg will be coadministered with erythromycin 500mg in the morning, and only erythromycin 500mg will be administered in the evening.

8.4.2.1 Day 26

The following procedures/assessments will be performed:

- C-SSRS prior to morning dosing
- Abbreviated physical exam prior to morning dosing
- Prior and concomitant medications recorded prior to morning dosing
- Vital signs (including systolic and diastolic BP, pulse rate, respiration rate, and oral temperature) prior to morning dosing
- Blood and urine samples for the following clinical laboratory tests will be collected prior to morning dosing:
  - Hematology, serum chemistry, and urinalysis
- Blood samples (venous and MITRA) for PK analysis (relative to morning dosing)
  - Predose
  - Postdose: 0.25h, 0.5h, 0.75h, 1h, 1.25h, 1.5h, 2h, 3h, 4h, 6h, 8h, and 12h
- Urine samples for PK analysis (relative to morning dosing)
  - Predose (≤1h before dosing)
  - Postdose: 0 to 12h
- Triplicate 12-lead ECGs
  - Morning dose: Predose,1h, 2h, 3h and 6h postdose
  - Evening dose: approximately 0.5h predose
- Recording of AEs/medical procedures

8.4.2.2 Day 27 to Day 32

The following procedures/assessments will be performed:

- C-SSRS prior to morning dosing
- Abbreviated physical examination prior to morning dosing
- Prior and concomitant medications recorded prior to morning dosing
- Vital signs (including systolic and diastolic BP, pulse rate, respiration rate, and oral temperature) prior to morning dosing
- Blood and urine samples for the following clinical laboratory tests will be collected (on Day 30 only):
  - Hematology, serum chemistry, and urinalysis
- Blood samples for PK trough analysis will be collected prior to morning dosing
- Urine samples for PK analysis (relative to morning dosing; see Section 8.4.2.1)

- Triplicate 12-lead ECGs
  - Morning dose: Predose,1h, 2h, 3h, and 6h postdose
  - Evening dose: approximately 0.5h predose
- Recording of AEs/medical procedures

8.4.2.3 Day 33

The following procedures/assessments will be performed:

- C-SSRS prior to morning dosing
- Abbreviated physical examination prior to morning dosing
- Prior and concomitant medications recorded prior to morning dosing
- Vital signs (including systolic and diastolic BP, pulse rate, respiration rate, and oral temperature) prior to morning dosing
- Blood and urine samples for the following clinical laboratory tests will be collected:
  - Hematology, serum chemistry, and urinalysis
- Blood samples (venous and MITRA) for PK analysis (relative to morning dosing)
  - Predose
  - Post last morning combination dose: 0.25h, 0.5h, 0.75h, 1h, 1.25h, 1.5h, 2h, 3h, 4h, 6h, 8h, 12h, 24h, 36h, 48h, 60h, 72h, 96h, and 120h
- Urine samples for PK analysis (relative to morning dosing)
  - Post last morning combination dose: 0 to 12h, 12h to 24h, 24h to 48h, 48h to 72h, and 72h to 96h
- Triplicate 12-lead ECGs
  - Morning dose: Predose, 1h, 2h, 3h, and 6h postdose
  - Evening dose: approximately 0.5h predose
- Recording of AEs/medical procedures

8.4.3 Treatment Period 3c (Day 34 to Day 38)

Study participants will be confined to the unit until Day 37 during Treatment Period 3c. During Treatment Period 3c, study participants will receive only erythromycin 500mg bid from Day 34 to Day 37. On Day 38, study participants will be discharged from the unit after completing the procedures and assessments.

8.4.3.1 Day 34 to Day 37

The following procedures/assessments will be performed:

- C-SSRS prior to morning dosing (Day 34 and Day 37 only)
- Abbreviated physical exam prior to morning dosing

- Prior and concomitant medications recorded prior to morning dosing
- Vital signs (including systolic and diastolic BP, pulse rate, respiration rate, and oral temperature) prior to morning dosing
- Blood and urine samples for the following clinical laboratory tests will be collected (on Day 37 only):
  - Serum pregnancy test (for women of childbearing potential only)
  - Hematology, serum chemistry, and urinalysis
- Blood (venous and MITRA) and urine samples for PK analysis (see Section 8.4.2.3)
- Triplicate 12-lead ECGs
  - Morning dose: Predose, 1h, 2h, 3h and 6h postdose
  - Evening dose: approximately 0.5h predose
- Recording of AEs/medical procedures

8.4.3.2 Day 38

The following procedures/assessments will be performed prior to discharge:

- Prior and concomitant medications
- C-SSRS
- Full physical exam
- Prior and concomitant medications
- Vital signs (including systolic and diastolic BP, pulse rate, respiration rate, and oral temperature)
- Triplicate 12-lead ECGs
- Blood samples (venous and MITRA) for PK analysis (see Section 8.4.2.3)
- Recording of AEs/medical procedures

After the procedures and assessments, study participants will be discharged from the unit provided there are no clinically significant safety issues that require extended supervision in the opinion of the Investigator.

8.5 Safety Follow-Up Period (7 to 10 days from final dose)

8.5.1 End of Study Visit (Day 44, Day 45, Day 46, or Day 47)

The following procedures/assessments will be performed 7 to 10 days after last dose of erythromycin or upon discontinuation of the study (EOS Visit):

- C-SSRS
- Full physical examination
- Prior and concomitant medications

- Vital signs (including systolic and diastolic BP, pulse rate, respiration rate, and oral temperature)
- Blood and urine samples for the following clinical laboratory tests will be collected:
  - Serum pregnancy test (for women of childbearing potential)
  - Hematology, serum chemistry, and urinalysis
- Triplicate 12-lead ECGs
- Recording of AEs/medical procedures

8.6 Withdrawal Visit

Study participants who withdraw from the study for any reason after the first dose, but prior to the SFU Visit, will be asked to return to the unit to complete a Withdrawal Visit (7 days ± 2 days, postdose). The same assessments as for the EOS Visit (see Section 8.5) will be performed. Study participants who withdraw between enrollment and first dose will be followed up only at the discretion of the Investigator.

8.7 Unscheduled visit

At the Investigator's discretion, an Unscheduled Visit may be completed at any time during the study if deemed necessary for the study participant's safety and wellbeing. The assessments to be conducted during an Unscheduled Visit will be based on the Investigator's judgement.

9 ASSESSMENT OF PHARMACOKINETIC VARIABLES

9.1 Pharmacokinetic variables

The PK variables are described in detail in Section 4.1. Calculations of PK variables will be made with Phoenix WinNonlin (version 6.3 or higher) using actual sampling times. The linear trapezoidal method will be used to calculate the AUC parameters. For details of PK analyses, refer to Section 12.3.

Detailed information on the collection, storage, preparation, and shipping of samples will be presented in a bioanalytical report.

9.2 Pharmacokinetic sampling procedures

Study participants are requested to provide blood samples for measurement of PSL levels using the VAMS technology on the MITRA microsampling device.

9.2.1 Blood pharmacokinetic sampling scheme

Serial blood samples for PK analysis of PSL and its metabolites (venous and MITRA) will be collected as described in Section 5.3 and Table 5-1.

The total blood volume collected for the study will not exceed 500mL per study participant.

Exact sampling times will be recorded in the eCRF.

All sample handling procedures, including the time of each sample collection, the start and stop time of centrifugation and placement into frozen storage (at the end of the sample workup), and

the date of transfer or shipment of the samples to the responsible analyst will be documented in detail.

Time deviations from scheduled sampling times will be discussed at the Data Review Meeting.

Full details of sample handling and processing are provided in the Laboratory Manual.

The maximum deviations from scheduled sampling times considered irrelevant for PK are defined in Table 9–1.

Table 9–1: Irrelevant time deviations for PK sampling

PK blood sampling times	Deviation from scheduled time considered irrelevant
0 hours (predose)	Within 60 minutes
0.25 to 1.5 hours	2 minutes
2 to 8 hours	5 minutes
12 hours	15 minutes
24 to 48 hours	60 minutes

PK=pharmacokinetic

9.2.2 Urine pharmacokinetic sampling scheme

Full details of urine collection will be available in the Laboratory Manual.

All aliquots will be stored pending potential assay for parent and metabolites depending on the outcome of the blood PK analysis.

9.3 Shipment procedures

Details of the PK samples labelling and shipment procedures will be provided in the Laboratory Manual.

9.4 Communication plan

A communication plan dedicated to PK laboratory activities (at the least) will be established in a separate document.

9.5 Bioanalytical method

Plasma concentration of PSL and metabolites will be determined with a validated bioanalytical method. Plasma and blood concentration of parent PSL collected by MITRA devices respectively will be determined with a scientific validated bioanalytical method.

10 ASSESSMENT OF SAFETY

10.1 Adverse events

10.1.1 Definitions

10.1.1.1 Adverse event

An AE is any untoward medical occurrence in a patient or clinical investigation study participant administered a pharmaceutical product that does not necessarily have a causal relationship with this treatment. An AE can therefore be any unfavorable and unintended sign (including an

abnormal laboratory finding), symptom, or disease temporally associated with the use of a medicinal (investigational) product, whether or not related to the medicinal (investigational) product.

In order to ensure complete safety data collection, all AEs occurring during the study (ie, after the signing of the ICF), including any pretreatment and posttreatment periods required by the protocol, must be reported in the eCRF even if no IMP was taken but specific study procedures were conducted. This includes all AEs not present prior to the initial visit and all AEs that recurred or worsened after the initial visit.

Signs or symptoms of the condition/disease for which the IMP is being studied should be recorded as AEs only if their nature changes considerably or their frequency or intensity increases in a clinically significant manner as compared to the clinical profile known to the Investigator from the study participant's history or Screening Period.

10.1.1.2 Serious adverse event

Once it is determined that a study participant experienced an AE, the seriousness of the AE must be determined. An SAE must meet 1 or more of the following criteria:

- Death
- Life-threatening

  (Life-threatening does not include a reaction that might have caused death had it occurred in a more severe form.)
- Significant or persistent disability/incapacity
- Congenital anomaly/birth defect (including that occurring in a fetus)
- Important medical event that, based upon appropriate medical judgment, may jeopardize the patient or study participant and may require medical or surgical intervention to prevent 1 of the other outcomes listed in the definition of serious

  (Important medical events may include, but are not limited to, potential Hy's Law [see Section 10.1.1.3], allergic bronchospasm requiring intensive treatment in an emergency room or at home, blood dyscrasias that do not result in inpatient hospitalization, or the development of drug dependency or drug abuse.)
- Initial inpatient hospitalization or prolongation of hospitalization

  (A patient admitted to a hospital, even if he/she is released on the same day, meets the criteria for the initial inpatient hospitalization. An emergency room visit that results in admission to the hospital would also qualify for the initial inpatient hospitalization criteria. However, emergency room visits that do not result in admission to the hospital would not qualify for this criteria and, instead, should be evaluated for 1 of the other criteria in the definition of serious [eg, life-threatening adverse experience, important medical event].

  Hospitalizations for reasons not associated with the occurrence of an AE [eg, preplanned surgery or elective surgery for a pre-existing condition that has not worsened or manifested in an unusual or uncharacteristic manner] do not qualify for reporting. For example, if a study participant has a condition recorded on his/her medical history and later has a preplanned surgery for this condition, it is not appropriate to record the surgery or

hospitalization as an SAE, since there is no AE upon which to assess the serious criteria. Please note that, if the pre-existing condition has worsened or manifested in an unusual or uncharacteristic manner, this would then qualify as an AE and, if necessary, the seriousness of the event would need to be determined).

10.1.1.2.1 Anticipated serious adverse events

No SAEs are anticipated to occur in the population studied in this protocol.

10.1.1.3 Adverse events of special interest

An AE of special interest is any AE that a regulatory authority has mandated be reported on an expedited basis, regardless of the seriousness, expectedness, or relatedness of the AE to the administration of a UCB product/compound. No AEs of special interest have been identified for PSL to date, with the exception of potential Hy's Law as described below.

Potential Hy's Law, defined as ≥3xULN ALT or AST with coexisting ≥2xULN total bilirubin in the absence of ≥2xULN ALP, with no alternative explanation for the biochemical abnormality, must ALWAYS be reported to UCB as an AE of special interest (ie, without waiting for any additional etiologic investigations to have been concluded). Follow-up information should then be reported if an alternative etiology is identified during investigation and monitoring of the study participant.

10.1.2 Procedures for reporting and recording adverse events

The study participant will be given the opportunity to report AEs spontaneously. A general prompt will also be given at each study visit to detect AEs. For example:

"Did you notice anything unusual about your health (since your last visit)?"

10.1.2.1 Description of adverse events

When recording an AE, the Investigator should use the overall diagnosis or syndrome using standard medical terminology, rather than recording individual symptoms or signs. The eCRF and source documents should be consistent. Any discrepancies between the study participant's own words on his/her own records (eg, diary card) and the corresponding medical terminology should be clarified in the source documentation.

Details for completion of the Adverse Event eCRF (including judgment of relationship to IMP) are described in the eCRF Completion Guidelines.

10.1.2.2 Rule for repetition of an adverse event

An increase in the intensity of an AE should lead to the repetition of the AE being reported with:

- The outcome date of the first AE that is not related to the natural course of the disease being the same as the start date of the repeated AE, and the outcome of "worsening"
- The AE verbatim term being the same for the first and repeated AE, so that the repeated AE can be easily identified as the worsening of the first one

10.1.2.3 Additional procedures for reporting serious adverse events

If an SAE is reported, UCB must be informed within 24 hours of receipt of this information by the site (see contact information for SAE reporting listed in the Serious Adverse Event Reporting

section at the front of the protocol). The Investigator must forward to UCB (or its representative) a duly completed "Investigator SAE Report Form for Development Drug" (SAE report form) provided by UCB, even if the data are incomplete, or if it is obvious that more data will be needed in order to draw any conclusions. Information recorded on this form will be entered into the global safety database.

An Investigator SAE report form will be provided to the Investigator. The Investigator SAE Report form must be completed in English.

It is important for the Investigator, when completing the SAE report form, to include the assessment as to a causal relationship between the SAE and the IMP administration. This insight from the Investigator is very important for UCB to consider in assessing the safety of the IMP and in determining whether the SAE requires reporting to the regulatory authorities in an expedited manner.

Additional information (eg, autopsy or laboratory reports) received by the Investigator must be provided within 24 hours. All documents in the local language must be accompanied by a translation in English, or the relevant information included in the same document must be summarized in the Investigator SAE report form.

The Investigator is specifically requested to collect and report to UCB (or its representative) any SAEs (even if the Investigator is certain that they are in no way associated with the IMP), up to 30 days from the end of the study for each study participant, and to also inform participating study participants of the need to inform the Investigator of any SAE within this period. Serious AEs that the Investigator thinks may be associated with the IMP must be reported to UCB regardless of the time between the event and the end of the study.

Upon receipt of the SAE report form, UCB will perform an assessment of expectedness of the reported SAE. The assessment of the expectedness of the SAE is based on the IB.

10.1.3 Follow up of adverse events

An AE should be followed until it has resolved, has a stable sequelae, the Investigator determines that it is no longer clinically significant, or the study participant is lost to follow up. This follow-up requirement applies to AEs, SAEs, and AEs of special interest; further details regarding follow up of PDILI events is provided in Section 10.2.1.4.

If an AE is ongoing at the end of the study for a study participant, follow up should be provided until resolution/stable level of sequelae is achieved, or until the Investigator no longer deems that it is clinically significant, or until the study participant is lost to follow up. If no follow up is provided, the Investigator must provide a justification. The follow up will usually be continued for 30 days after the study participant has discontinued his/her IMP.

Information on SAEs obtained after clinical database lock will be captured through the Patient Safety (PS) database without limitation of time.

10.1.4 Pregnancy

If an Investigator is notified that a study participant has become pregnant after the first intake of any IMP, the Investigator must immediately notify UCB's PS department by providing the completed Pregnancy Report and Outcome form (for contact details see Serious Adverse Event reporting information at the beginning of this protocol). The study participant should be

withdrawn from the study as soon as pregnancy is known (by positive pregnancy test), and the following should be completed:

- The study participant should immediately stop the intake of the IMP.
- The study participant should return for an EOS Visit 7 to 10 days after the study participant has discontinued her IMP.

The Investigator must inform the study participant of information currently known about potential risks and about available treatment alternatives.

The pregnancy will be documented on the Pregnancy Report and Outcome form provided to the Investigator. The progression of the pregnancy and the eventual birth (if applicable) must be followed up using the Pregnancy Report and Outcome form in which the Investigator has to report on the health of the mother and of the child. Every reasonable attempt should be made to follow the health of the child for 30 days after birth for any significant medical issues. In certain circumstances, UCB may request that follow up is continued for a period longer than 30 days. If the study participant is lost to follow up and/or refuses to give information, written documentation of attempts to contact the study participant needs to be provided by the Investigator and filed at the site. UCB's PS department is the primary contact for any questions related to the data collection for the pregnancy, eventual birth, and follow up.

In cases where the partner of a male study participant enrolled in a clinical study becomes pregnant, the Investigator or designee is asked to contact the study participant to request consent of the partner via the Partner Pregnancy Consent form that has been approved by the responsible IEC and should be available in the Investigator site file. In case of questions about the consent process, the Investigator may contact Parexel/Hammersmith Medicines Research contract monitor for the study. The Investigator will complete the Pregnancy Report and Outcome form and send it to UCB's PS department (for contact details see Serious Adverse Event reporting information at the beginning of this protocol) only after the partner has agreed that additional information can be captured and has provided the signed Partner Pregnancy Consent form. UCB's PS department is also the primary contact for any questions related to the data collection for the partner pregnancy, eventual birth, and follow up.

A pregnancy becomes an SAE in the following circumstances: miscarriage, abortion (elective or spontaneous), unintended pregnancy after hormonal contraceptive failure (if the hormonal contraceptive was correctly used), ectopic pregnancy, fetal demise, or any congenital anomaly/birth defect of the baby. Those SAEs must be additionally reported using the Investigator SAE Report form.

10.1.5 Suspected transmission of an infectious agent via a medicinal product

For the purposes of reporting, any suspected transmission of an infectious agent via a medicinal product should be considered as an SAE; such cases must be reported immediately, recorded in the AE module of the eCRF, and followed as any other SAE. Any organism, virus, or infectious particle (eg, prion protein transmitting transmissible spongiform encephalopathy), pathogenic or nonpathogenic, is considered an infectious agent.

10.1.6 Overdose of investigational medicinal product

Excessive dosing (beyond that prescribed in the protocol and including overdose) should be recorded in the eCRF. Any SAE or nonserious AE associated with excessive dosing must be followed as any other SAE or nonserious AE. These events are only considered AEs or SAEs if there are associated clinical signs and symptoms or if the act of taking the excess medicine itself is an AE or SAE (eg, suicide attempt).

10.1.7 Safety signal detection

Selected data from this study will be reviewed periodically to detect as early as possible any safety concern(s) related to the IMP so that Investigators, clinical study participants, regulatory authorities, and IECs will be informed appropriately and as early as possible.

The Sponsor Study Physician or medically qualified designee/equivalent will conduct an ongoing review of SAEs and perform ongoing SAE reconciliations in collaboration with the PS representative.

As appropriate for the stage of development and accumulated experience with the IMP, medically qualified personnel at UCB may identify additional safety measures (eg, AEs, vital signs, laboratory or ECG results) for which data will be periodically reviewed during the course of the study.

10.2 Laboratory measurements

Blood and urine samples will be taken for clinical laboratory assessments at the time points specified in Table 5-1.

A urine drug screen, cotinine urine screen, and alcohol breath test will be performed at the Screening Visit (Day -28 to Day -2) and before study participants are admitted to the unit on Day -2, Day 10, and Day 21. Serology will be performed at the Screening Visit to assess study participant eligibility. A serum pregnancy test will be performed at the Screening Visit, Day -2, Day 10, Day 21, Day 37, and the SFU Visit.

Laboratory safety measurements will be performed after a fasting period of at least 4 hours only at the Screening Visit. Clinical laboratory parameters to be measured are presented in Table 10-1.

Sampling time and last AED intake should be recorded in the eCRF.

Table 10-1: Laboratory measurements

Laboratory assessment	Parameters
Hematology	Hemoglobin, hematocrit, red blood cell count, mean corpuscular volume, platelets, total white blood cell count, and differential consisting of absolute counts and percentages of the following leukocyte types: neutrophils, lymphocytes, monocytes, eosinophils, and basophils
Biochemistry	Sodium, potassium, calcium, inorganic phosphorous, glucose (fasting, only at Screening), urea, creatinine, total bilirubin (conjugated bilirubin when total bilirubin is outside the reference range), total protein, albumin, ALT, AST, and ALP
Viral serology (only at Screening Visit)	HIV-1/2Ab, HBsAg, and HCV-Ab
Pregnancy	Serum pregnancy test
Urinalysis	Specific gravity, pH, glucose (fasting, only at Screening), protein, blood, leukocytes, nitrite, ketones, bilirubin, urobilinogen (with dipstick) If protein, blood, or leukocytes are abnormal (positive), a microscopic examination of the sediment will be performed.
Drug screen	Amphetamines/methamphetamines, benzodiazepines, barbiturates, cocaine, cannabis, methadone, tricyclic antidepressants, and opiates

ALP=alkaline phosphatase; ALT=alanine aminotransferase; AST=aspartate aminotransferase; HBsAG=hepatitis B surface antigen; HCV-Ab=hepatitis C antibody; HIV-1/2Ab=human immunodeficiency virus-1/2 antibodies; SFU=Safety Follow-Up

10.2.1 Evaluation of potential drug-induced liver injury

The PDILI IMP discontinuation criteria for this study are provided in Section 6.4.1, with the accompanying required follow-up investigation and monitoring detailed below. All PDILI events must be reported as an AE and reported to the study site and Sponsor within 24 hours of learning of their occurrence. Any PDILI event that meets the criterion for potential Hy's Law must be reported as an AE of special interest (see Section 10.1.1.3), and, if applicable, also reported as an SAE (see Section 10.1.1.2).

Evaluation of PDILI consists of the diagnostic testing and continued monitoring included in Table 10–2 (specific tests dependent on laboratory results and corresponding symptoms) and consultation with a local hepatologist (if applicable; discussed in Section 10.2.1.1). The local hepatologist is the expert usually consulted by the treating physician for assessment and management of potential hepatic disease. This would usually be a hepatologist, but may be a gastroenterologist. Additional investigation and monitoring may be required and adapted based on the diagnosis after the cause of the liver injury/abnormality is confirmed (details in Section 10.2.1.4).

The results of all monitoring, including laboratory testing and other testing, should be made available to the study site and Sponsor.

All initial tests resulting in abnormal hepatic laboratory values need to be repeated, but appropriate medical action must not be delayed waiting for the repeat result.

When IMP is discontinued, all concomitant medications and herbal supplements that are not medically necessary should also be discontinued. In these cases, the Investigator should also consider dose reduction for medically necessary concomitant medication and consider changing any medically required concomitant medication known to be hepatotoxic to a suitable alternative.

When IMP is stopped due to PDILI (as described in Section 6.4.1), IMP must be permanently discontinued unless a subsequent alternative diagnosis fully explains the hepatic findings.

Rechallenge with a substance potentially causing drug-induced liver injury is dangerous, may be fatal, and must not occur.

The table below summarizes the approach to investigate PDILI.

Table 10–2: Required investigations and follow up for PDILI

Laboratory value					
ALT or AST	**Total bilirubin**	**Symptoms [a] of hepatitis or hypersensitivity**	**Consultation requirements**	**Required testing**	**Continued evaluation**
Requires immediate and permanent IMP discontinuation					
≥3xULN	<2xULN	No	Medical Monitor must be notified within 24 hours (eg, by laboratory alert) and study participant discussed with Medical Monitor ASAP.	Must have repeat liver chemistry values and additional testing completed ASAP (see Section 10.2.1.3); recommended to occur within 24 hours at Phase 1 unit or with HCP.	Monitoring of liver chemistry values required once per week until values normalize, stabilize, or return to within Baseline values. [b]
≥3xULN	NA	Yes	Hepatology consult. [c] Medical Monitor must be notified within 24 hours (eg, by laboratory alert) and study participant discussed with Medical Monitor ASAP.		Monitoring of liver chemistry values required at least twice per week until values normalize, stabilize, or return to within Baseline values. [b]
≥3xULN	≥2xULN [d]	NA			

ALP=alkaline phosphatase; ALT=alanine aminotransferase; ASAP=as soon as possible; AST=aspartate aminotransferase; HCP=healthcare practitioner; IMP=investigational medicinal product; NA=not applicable; PDILI=potential drug-induced liver injury; ULN=upper limit of normal

[a] Hepatitis symptoms include fatigue, nausea, vomiting, and right upper quadrant pain or tenderness; hypersensitivity symptoms include eosinophilia (>5%), rash, and fever (without clear alternative cause).

[b] Unless an alternative monitoring schedule is agreed by the Investigator and UCB responsible physician. Determination of stabilization is at the discretion of the Investigator in consultation with the hepatologist (as applicable) and UCB responsible physician, as needed.

[c] Details provided in Section 10.2.1.1. The local hepatologist is the expert usually consulted by the treating physician for assessment and management of potential hepatic disease. This would usually be a hepatologist, but may be a gastroenterologist.

[d] If the study participant also has ≥2xULN ALP, the possibility of an indication of biliary obstruction should be discussed with the Medical Monitor.

10.2.1.1 Consultation with Medical Monitor and local hepatologist

Potential drug-induced liver injury events require notification of the Medical Monitor within 24 hours (eg, by laboratory alert), and the study participant must be discussed with the Medical Monitor as soon as possible. If required, the study participant must also be discussed with the local hepatologist. The local hepatologist is the expert usually consulted by the treating physician for assessment and management of potential hepatic disease. This would usually be a hepatologist, but may be a gastroenterologist. If determined necessary, this discussion should be followed by a full hepatology assessment (see Section 10.2.1.3) and SAE report (if applicable).

10.2.1.2 Immediate action: determination of investigational medicinal product discontinuation

All PDILI events require immediate action, testing, and monitoring.

The immediate action is dependent on the laboratory values and symptoms of hepatitis or hypersensitivity and requires permanent IMP discontinuation (see Section 6.4.1 and Table 10–2 for details).

When IMP is discontinued, all concomitant medications and herbal supplements that are not medically necessary should also be discontinued. The Investigator should also consider dose reduction for medically necessary concomitant medication and consider changing any medically required concomitant medication known to be hepatotoxic to a suitable alternative.

10.2.1.3 Testing: identification/exclusion of alternative etiology

The measurements and additional information required for the assessment of PDILI events when there is a reasonable possibility that they may have been caused by the IMP are detailed in Table 10–3 (laboratory measurements) and Table 10–4 (additional information). Results of the laboratory measurements and information collected are to be submitted to the Sponsor on the corresponding eCRF. If the medical history of the study participant indicates a requirement for other assessments not included below, these additional assessments should be completed and submitted, as applicable.

The following measurements are to be assessed:

Table 10–3: PDILI laboratory measurements

Virology-related	Hepatitis A IgM antibody
	HBsAg
	Hepatitis E IgM antibody
	HBcAb-IgM
	Hepatitis C RNA
	Cytomegalovirus IgM antibody
	Epstein-Barr viral capsid antigen IgM antibody (if unavailable, obtain heterophile antibody or monospot testing)
Immunology	Anti-nuclear antibody (qualitative and quantitative)
	Anti-smooth muscle antibody (qualitative and quantitative)
	Type 1 anti-liver kidney microsomal antibodies (qualitative and quantitative)
Hematology	**Eosinophil count**
Urinalysis	**Toxicology screen**
Chemistry	Amylase
	If total bilirubin ≥1.5xULN, obtain fractionated bilirubin to obtain % direct bilirubin
	Serum CPK and LDH to evaluate possible muscle injury causing transaminase elevation
Additional	Prothrombin time/INR [a]
	Serum pregnancy test
	PK sample

ALT=alanine aminotransferase; CPK=creatine phosphokinase; HBcAb-IgM=hepatitis B core antibody-IgM; HBsAg=hepatitis B surface antigen; IgM=immunoglobulin M; INR=international normalized ratio; LDH=lactate dehydrogenase; PDILI=potential drug-induced liver injury; PK=pharmacokinetic; RNA=ribonucleic acid; ULN=upper limit of normal

[a] Measured only for study participants with ALT >8xULN, elevations in total bilirubin, and symptoms of hepatitis or hypersensitivity. Hepatitis symptoms include fatigue, nausea, vomiting, and right upper quadrant pain or tenderness; hypersensitivity symptoms include eosinophilia (>5%), rash, and fever (without clear alternative cause).

The following additional information is to be collected:

Table 10–4: PDILI information to be collected

New or updated information
Concomitant prescription and over-the-counter medications (eg, acetaminophen, herbal remedies, vitamins); dosages and dates should be included.
Pertinent medical history, including the following: • History of liver disease (eg, autoimmune hepatitis, nonalcoholic steatohepatitis or other "fatty liver disease") • Adverse reactions to drugs • Allergies • Relevant family history or inheritable disorders (eg, Gilbert's syndrome, alpha-1 antitrypsin deficiency) • Recent travel • Progression of malignancy involving the liver (Note: Metastatic disease to the liver, by itself, should not be used as an explanation for significant AST and/or ALT elevations.)
The appearance or worsening of clinical symptoms of hepatitis or hypersensitivity (eg, fatigue, nausea, vomiting, right upper quadrant pain or tenderness, decreased appetite, abdominal pain, jaundice, fever, or rash)
Recent clinically significant hypotension or hypoxemia with compromised cardiopulmonary function
Alcohol and illicit drug use
Results of liver imaging or liver biopsy, if done
Results of any specialist or hepatology consult, if done
Any postmortem/pathology reports

ALT=alanine aminotransferase; AST=aspartate aminotransferase; PDILI=potential drug-induced liver injury

10.2.1.4 Follow-up evaluation

Potential drug-induced liver injury events require follow-up monitoring as described in Table 10–2. Monitoring should continue until liver chemistry values normalize, stabilize, or return to baseline. Determination of stabilization is at the discretion of the Investigator in consultation with the hepatologist (as applicable) and UCB responsible physician, as needed.

10.2.1.5 Optional hepatic investigation sample collection

If a study participant is undergoing further investigation for PDILI and has consented to retrospective genetic analysis per local regulations, the study participant's blood sample will be shipped to a secure storage facility. The blood sample will be retained in the UCB Hepatic Investigation Biobank to solely support retrospective genetic analyses associated with an adverse therapeutic response to PSL.

Genetic analyses of deoxyribonucleic acid isolated from the blood will be contracted by UCB to specialized third-party laboratories and analysis will be limited to:

- Uridine 5′-diphospho-glucuronosyltransferase loci − the loci responsible for Gilbert's syndrome (hyperbilirubinemia)
- Human leukocyte antigen (HLA) loci − for example, HLA-B5701 that has been associated with abacavir- and flucloxacillin-induced liver injury
- Absorption, distribution, metabolism, and excretion gene loci associated with abnormal pharmacokinetics

Genetic analysis of samples may be performed immediately, on a per-study basis, or as part of combined analyses across multiple studies belonging to the same clinical development program. As a result, samples will be retained for 15 years unless clinical development of the IMP is terminated, at which point all samples will be destroyed. The results determined using clinically approved diagnostic tests will be made available to the Investigator upon request.

Study participants may request at any time that their sample be removed from the UCB Hepatic Investigation Biobank and destroyed, though data from analyses already performed will remain on file. All samples, associated materials, and data will be kept securely by UCB and its agents. A sample destruction request should be made in writing to the Investigator who will notify the UCB Biorepository Manager (Global Exploratory Development, UCB, Slough, SL1 3WE, United Kingdom).

10.3 Other safety measurements

10.3.1 Physical examination

Full physical examinations will be performed at the time points specified in Table 5-1. Full physical examinations will include cardiac and respiratory function via auscultation and review of the following body systems: general appearance; ear, nose, and throat; eyes; hair and skin; respiratory; cardiovascular; gastrointestinal; musculoskeletal; hepatic; neurological; and mental status.

Abbreviated physical examinations will be performed at the time points specified in Table 5-1. These abbreviated physical examinations will include a review of the following body systems: general appearance; skin; respiratory; cardiovascular; gastrointestinal; hepatic; and mental status.

Height (study participant without shoes, and height rounded to the nearest 0.5cm) and body weight (study participant in underwear or light clothing, without shoes and rounded to the nearest 0.1kg) will be recorded at the Screening Visit and BMI will be derived (weight (kg)/[height (m)]^2).

10.3.2 Vital signs

Vital signs (pulse rate, BP, respiratory rate, and body temperature) will be recorded at the time points shown in Table 5-1.

For the purposes of assessing the inclusion criterion, at the Screening Visit and the Baseline Visit, BP measurements will be performed in both supine and standing positions according to the following procedure: Measure supine BP after the study participant has been lying down for 10 minutes, then ask the study participant to stand up and record the standing BP

after 1 minute and 3 minutes. At all time points after the Screening Visit, BP will only be measured in the supine position, ie, there will be no assessment for orthostatic hypotension.

By decision of the Sponsor and the Investigator, the time points specified in Table 5-1 may be modified based on preliminary safety and PK assessments from previous doses tested in the study.

10.3.3 Standard 12-lead electrocardiogram

Triplicate standard 12-lead ECGs (RR interval, PR interval, QRS interval, QT, QTcB, and QTcF) will be recorded at times specified in Table 5-1, according to the following procedure: study participant lies in a supine position for ≥5 minutes; then a 12-lead ECG will be recorded in the same position. All ECG recordings will be performed in triplicate at 2- to 3-minute intervals.

Electrocardiograms will be recorded at a speed of 25mm/s and with a calibration of 1cm/mV.

The times specified in Table 5-1 include a series of 'triplicate 12-lead ECG run-in days' to be performed 1 day prior to first PSL or erythromycin dose in Treatment Periods 1, 2, and 3 (that is, Day -1, Day 11, Day 22, and Day 25). On these days, triplicate standard 12-lead ECGs will be performed for each of the following matching time points: predose, 1h, 2h, 3h, and 6h postdose for the morning administration of PSL and/or erythromycin, and 0.5h predose for the evening administration of PSL and/or erythromycin.

By decision of the Sponsor and the Investigator, the time points specified in Table 5-1 may be modified based on preliminary safety and PK assessments from previous doses tested in the study.

The Investigator or designee will determine whether the results of the ECG are normal or abnormal. All important abnormalities should be reported. The original ECG tracing will be signed or initialled, and dated by the Investigator or designee, and will be retained at the clinical site as part of the Investigator's Site File. The original electronic file of the ECG tracing will be transferred to UCB and will remain available at least until the approval of the clinical study report.

10.3.4 Assessment of suicidality

The C-SSRS will be completed at the scheduled time points presented in Table 5-1.

Suicidality will be assessed by trained study personnel using the C-SSRS (Posner et al, 2011). This scale will be used for screening as well as to assess suicidal ideation and behavior that may occur during the study. The Investigator's decision about study participant continuation in the study or study participant withdrawal from the study if the study participant has a positive response to the CSSRS Question 4, should be based on the benefit/risk balance for continuation or discontinuation of study treatment in view of the individual study participant circumstances, condition, attained efficacy, causality, alternative risk management options, etc.

If an additional visit (or unscheduled visit) is conducted due to safety or efficacy reasons, a C-SSRS assessment will be performed with the study participant during the visit. If an additional visit (or unscheduled visit) is conducted for reasons other than safety or efficacy concerns (eg, replacement of lost medication, repeated collection of a laboratory specimen due to collection or analysis issues), a C-SSRS will not be required at these visits.

Details of the case must be documented by the Investigator (PI or designee, not site staff conducting the C-SSRS) and provided to UCB via the SAE reporting process.

11 STUDY MANAGEMENT AND ADMINISTRATION

11.1 Adherence to protocol

The Investigator should not deviate from the protocol. However, the Investigator should take any measure necessary in deviation from or not defined by the protocol in order to protect clinical study participants from any immediate hazard to their health and safety. In this case, this action should be taken immediately, without prior notification of the regulatory authority, IEC, or Sponsor.

After implementation of such measure, the Investigator must notify the Exploratory Project Manager of the Sponsor within 24 hours and follow any local regulatory requirements.

11.2 Monitoring

UCB (or designee) will monitor the study to meet the Sponsor's monitoring SOPs, ICH-GCP guideline, and applicable regulatory requirements, and to ensure that study initiation, conduct, and closure are adequate. Monitoring of the study may be delegated by UCB to a CRO or a contract monitor.

The Investigator and his/her staff are expected to cooperate with UCB (or designee) and to be available during the monitoring visits to answer questions sufficiently and to provide any missing information. The Investigator(s)/institution(s) will permit direct access to source data/documents for study-related monitoring, audits, IEC review, and regulatory inspection(s).

The Investigator will allow UCB (or designee) to periodically review all eCRFs and corresponding source documents (eg, hospital and laboratory records for each study participant). Monitoring visits will provide UCB (or designee) with the opportunity to evaluate the progress of the study, verify the accuracy and completeness of eCRFs, ensure that all protocol requirements, applicable authorities regulations, and Investigator's obligations are being fulfilled, and resolve any inconsistencies in the study records.

11.2.1 Definition of source data

All source documents must be accurate, clear, unambiguous, permanent, and capable of being audited. They should be made using some permanent form of recording (ink, typing, printing, optical disc). They should not be obscured by correction fluid or have temporary attachments (such as removable self-stick notes).

Source documents are original records in which raw data are first recorded. These may include hospital/clinic/general practitioner records, charts, diaries, x-rays, laboratory results, printouts, pharmacy records, care records, ECG or other printouts, completed scales, or quality of life questionnaires, for example. Source documents should be kept in a secure, limited access area.

Source documents that are computer generated and stored electronically must be printed for review by the monitor (eg, ECG reports). Once printed, these copies should be signed and dated by the Investigator and become a permanent part of the study participant's source documents. The Investigator will facilitate the process for enabling the monitor to compare the content of the printout and the data stored in the computer to ensure all data are consistent.

Electronic data records, such as Holter monitor records or electroencephalogram records, must be saved and stored as instructed by UCB (or designee).

11.2.2 Source data verification

Source data verification ensures accuracy and credibility of the data obtained. During monitoring visits, reported data are reviewed with regard to being accurate, complete, and verifiable from source documents (eg, study participant files, recordings from automated instruments, tracings [ECG], x-ray films, laboratory notes). All data reported on the eCRF should be supported by source documents, unless otherwise specified in Section 11.2.1.

11.3 Data handling

11.3.1 Case Report form completion

The Investigator is responsible for prompt reporting of accurate, complete, and legible data in the eCRFs and in all required reports.

Any change or correction to the eCRF after saving must be accompanied by a reason for the change.

Corrections made after the Investigator's review and approval (by means of a password/electronic signature) will be reapproved by the Investigator.

The Investigator should maintain a list of personnel authorized to enter data into the eCRF.

Detailed instructions will be provided in the eCRF Completion Guidelines.

11.3.2 Database entry and reconciliation

Electronic Case Report forms/external electronic data will be entered/loaded into a validated electronic database using a clinical data management system (CDMS). Computerized data cleaning checks will be used in addition to manual review to check for discrepancies and to ensure consistency of the data. Case Report form data are entered into the clinical database using independent, double-data entry, with the exception of comment fields, which are verified by a second person. The data are entered into the eCRFs once and are subsequently verified if the study is performed using electronic data capture.

An electronic audit trail system will be maintained within the CDMS to track all data changes in the database once the data have been saved initially into the system or electronically loaded. Regular backups of the electronic data will be performed.

11.3.3 Study Participant Screening and Enrollment log/Study Participant Identification Code list

The study participant's screening and enrollment will be recorded in the Study Participant Screening and Enrollment Log.

The Investigator will keep a Study Participant Identification Code list. This list remains with the Investigator and is used for unambiguous identification of each study participant.

The study participant's consent and enrollment in the study must be recorded in the study participant's medical record. These data should identify the study and document the dates of the study participant's participation.

11.4 Termination of the study

UCB reserves the right to temporarily suspend or prematurely discontinue this study either at a single site, multiple sites, or at all sites at any time for reasons including, but not limited to, safety or ethical issues, inaccurate or incomplete data recording, noncompliance, or unsatisfactory enrollment with respect to quality or quantity.

If the study is prematurely terminated or suspended, UCB (or its representative) will inform the Investigators/institutions and the regulatory authority(ies) of the termination or suspension and the reason(s) for the termination or suspension, in accordance with applicable regulatory requirement(s). The IEC should also be informed and provided with reason(s) for the termination or suspension by the Sponsor or by the Investigator/institution, as specified by the applicable regulatory requirement(s). In addition, arrangements will be made for the return of all unused IMP and other material in accordance with UCB procedures for the study.

11.5 Archiving and data retention

The Investigator will maintain adequate records for the study, including eCRFs, medical records, laboratory results, Informed Consent documents, drug dispensing and disposition records, safety reports, information regarding participants who discontinued, and other pertinent data.

All essential documents are to be retained by the Investigator until at least 2 years after the last approval of a marketing application in an ICH region and until there are no pending or contemplated marketing applications in an ICH region, or at least 2 years have elapsed since the formal discontinuation of clinical development of the IMP. These documents should be retained for a longer period, however, if required by the applicable regulatory requirement(s) or by an agreement with UCB (Committee for Proprietary Medicinal Products [CPMP]/ICH/135/95, 2002 [Section 4.9.5]). The Investigator will contact UCB for authorization prior to the destruction of any study records or in the event of accidental loss or destruction of any study records. The Investigator will also notify UCB should he/she relocate or move the study-related files to a location other than that specified in the Sponsor's Study Master File.

11.6 Audit and inspection

The Investigator will permit study-related audits mandated by UCB, after reasonable notice, and inspections by domestic or foreign regulatory authorities.

The main purposes of an audit or inspection are to confirm that the rights and wellbeing of the study participants enrolled have been protected, that enrolled study participants (ie, signing consent and undergoing study procedures) are appropriate for the study, and that all data relevant for the evaluation of the IMP have been processed and reported in compliance with the planned arrangements, the protocol, investigational site, and IEC SOPs, ICH GCP, and applicable regulatory requirements.

The Investigator will provide direct access to all study documents, source records, and source data. If an inspection by a regulatory authority is announced, the Investigator will immediately inform UCB (or designee).

11.7 Good Clinical Practice

Noncompliance with the protocol, ICH-GCP, or local regulatory requirements by the Investigator, institution, institution staff, or designees of the Sponsor will lead to prompt action

by UCB to secure compliance. Continued noncompliance may result in the termination of the site's involvement in the study.

12 STATISTICS

A description of statistical methods follows and will be described in more detail in the Statistical Analysis Plan (SAP).

12.1 Definition of analysis sets

12.1.1 Enrolled Set

The Enrolled Set (ES) consists of all study participants who have signed the ICF.

12.1.2 Full Analysis Set

The Full Analysis Set (FAS) consists of all study participants who have signed the ICF form and received IMP. Analysis of this set will be according to the treatment the study participants actually received.

All safety analyses will be performed using the FAS. All safety variables will be summarized by treatment (PSL alone, erythromycin alone, PSL+erythromycin, and the SFU).

12.1.3 Pharmacokinetic Per-Protocol Set

The Pharmacokinetic Per-Protocol Set (PK-PPS) is a subset of the FAS, consisting of those study participants who had no important protocol deviations affecting the PK parameters and for whom a sufficient number of samples are available to determine at least 1 PK parameter.

12.2 General statistical considerations

Summary statistics will be provided for all safety and Baseline/demographic variables. The datasets will follow the UCB analysis data model (ADaM) data specifications. All analyses will be performed using SAS® version 9.4 or later (SAS Institute, Cary, NC, USA). The PK noncompartmental analysis (NCA) will be performed using Pharsight Phoenix® WinNonlin® v6.3 (or higher). Categorical endpoints will be summarized using number of participants, frequency, and percentages. Missing data will not be imputed. For continuous variables, descriptive statistics (number of available observations, mean, median, standard deviation [SD], minimum, and maximum will be tabulated.

12.3 Planned pharmacokinetic and other analyses

12.3.1 Analysis of the primary pharmacokinetic variables

Pharmacokinetics will be determined using the PK-PPS.

Pharmacokinetic parameters of PSL and metabolites will be calculated by using the actual blood sampling time points.

The plasma concentration time profiles (and urine amounts) and PK parameters of PSL and metabolites will be summarized by treatment periods using descriptive statistics (number of available observations, arithmetic mean, SD, geometric mean, coefficient of variation of the geometric mean, median, minimum, and maximum). Values below the lower limit of quantification (LLOQ) will be reported with a clear sign indicating that they were below the

LLOQ. Descriptive statistics of concentrations will be calculated if at least two-thirds of the individual data points are quantifiable (≥LLOQ).

Individual plasma PSL and metabolites concentration time profiles will be displayed graphically on a linear-linear scale and semi-logarithmic scale (including spaghetti plots). Geometric mean plasma concentrations-time curves including 95% confidence intervals (CIs) will be displayed by treatment period (without/with erythromycin).

The similarity of PK parameters for PSL and its metabolites (C_{max}, $AUC_{(0-12)}$,$C_{max,ss}$, and AUC_{τ}) between periods with erythromycin and without erythromycin will be assessed within the analysis of variance (ANOVA) using data from the 3 treatment periods as follows: point estimates for the ratio of geometric means between with and without erythromycin and the respective 2-sided 90% CIs will be computed using the least squares means and the root mean squares of error from the ANOVA of the log-transformed data with subsequent exponential transformation. Inter-study participant and intra-study participant variability on PK parameters for PSL and its metabolites will be derived from these analyses. Ping pong plots will be displayed.

The PSL concentrations and PK parameters obtained from MITRA microsampling method will be compared to those of the conventional venous sampling method using descriptive analysis (tables with summary statistics and graphs).

12.3.2 Safety analyses

All safety analyses will be performed using the study participants in the FAS.

All AEs will be coded using the Medical Dictionary for Regulatory Activities (MedDRA®) and characterized as pre-treatment and treatment-emergent according to the intake of the IMP.

The occurrence and incidence of treatment-emergent adverse events (TEAEs) will be summarized by MedDRA system organ class and preferred term, by treatment periods, by treatment, and by treatment within treatment periods (for Treatment Period 3b). The occurrence and incidence of TEAEs will also be summarized by intensity and by relationship to the IMP as judged by the Investigator. Adverse events leading to discontinuation and SAEs will also be summarized.

Laboratory variables and changes from Baseline (during the Screening Period) will be summarized by descriptive statistics at each time point by treatment periods. Shift tables from Baseline to each post-Baseline time point will be presented by treatment periods. Values outside the reference range will be flagged in the listings. Any PDILI events will be listed.

Vital sign variables (BP, PR, oral body temperature, and respiration rate) and changes from Baseline (predose of each treatment period) will be summarized by descriptive statistics at each time point by treatment periods.

Electrocardiograms will be recorded 3 times at each time point. The individual mean at each time point will be calculated as raw parameters for descriptive analysis. The-individual mean and change from baseline (time-matched Baseline day of each treatment period, when applicable) will be summarized by descriptive statistics at each time point by treatment periods.

Physical examination abnormalities and C-SSRS data will be listed.

12.4 Handling of protocol deviations

Important protocol deviations (IPDs) are deviations from the protocol that potentially could have a meaningful impact on the primary objective of the study. The criteria for identifying such protocol deviations will be defined within the relevant protocol deviation specification document, which is part of the data cleaning plan. The IPDs will be reviewed as part of the ongoing data cleaning process and data evaluation. After all data have been verified/coded/entered into a database, a data evaluation meeting (DEM) will be performed. The purpose of this review will be to check all protocol deviations and the quality of the data. The review will also help guide the decision how to manage problems in the study participants' data (eg, withdrawals, dropouts, and protocol deviations).

Accepted deviations from theoretical time points will be described in the appropriate documents and included in the Study Master File. After the data review, resolution of all issues, and documentation of all decisions, the database will be locked.

12.5 Handling of dropouts or missing data

The methods for handling dropouts and missing data will be described in the SAP.

12.6 Planned interim analysis and data monitoring

There is no interim analysis planned for this study.

12.7 Determination of sample size

Using SimCYP simulations data, a sample size of 20 healthy study participants is needed to assess the PK interaction between PSL and erythromycin, and to estimate the mean PSL AUC_{τ} ratio of with/without erythromycin of 3.2 with a half-width of the CI of 0.75.

This sample size has been evaluated with a conditional probability of 80%, assuming an inter-participant coefficient of variation of 140%, correlation of 0.5, 2-sided and $\alpha = 0.05$.

A sufficient number of healthy study participants (up to 28) will be selected to have 20 completed study participants.

13 ETHICS AND REGULATORY REQUIREMENTS

13.1 Informed consent

Study participant's informed consent must be obtained and documented in accordance with local regulations, ICH-GCP requirements, and the ethical principles that have their origin in the principles of the Declaration of Helsinki.

Prior to obtaining informed consent, information should be given in a language and at a level of complexity understandable to the study participant in both oral and written form by the Investigator (or designee). Each study participant will have the opportunity to discuss the study and its alternatives with the Investigator.

Prior to participation in the study, the ICF should be signed and personally dated by the study participant, or his/her legal representative, and by the person who conducted the informed consent discussion (Investigator or designee). The study participant or his/her legal representative must receive a copy of the signed and dated ICF. As part of the consent process,

each study participant must consent to direct access to his/her medical records for study-related monitoring, auditing, IEC review, and regulatory inspection.

If the ICF is amended during the study, the Investigator (or the Sponsor, if applicable) must follow all applicable regulatory requirements pertaining to the approval of the amended ICF by the IEC and use of the amended form.

The study participant may withdraw his/her consent to participate in the study at any time. A study participant is considered as enrolled in the study when he/she has signed the ICF. An eCRF must not be started, nor may any study specific procedure be performed for a given study participant, without having obtained his/her written consent to participate in the study.

13.2 Study participant identification cards

Upon signing the Informed Consent and Assent form (as applicable), the study participant or legal representative will be provided with a study participant identification card in the language of the study participant. The Investigator will fill in the study participant identifying information and medical emergency contact information. The Investigator will instruct the study participant to keep the card with him/her at all times.

13.3 Independent Ethics Committee

The study will be conducted under the auspices of an IEC, as defined in local regulations, ICH-GCP, and in accordance with the ethical principles that have their origin in the Declaration of Helsinki.

The Investigator/UCB will ensure that an appropriately constituted IEC that complies with the requirements of the current ICH-GCP version or applicable country-specific regulations will be responsible for the initial and continuing review and approval of the clinical study. Prior to initiation of the study, the Investigator/UCB will forward copies of the protocol, ICF, IB, Investigator's curriculum vitae (if applicable), advertisement (if applicable), and all other study participant-related documents to be used for the study to the IEC for its review and approval.

Before initiating a study, the Investigator will have written and dated full approval from the responsible IEC for the protocol.

The Investigator will also promptly report to the IEC all changes in the study, all unanticipated problems involving risks to human study participants or others, and any protocol deviations, to eliminate immediate hazards to study participants.

The Investigator will not make any changes in the study or study conduct without IEC approval, except where necessary to eliminate apparent immediate hazards to the study participants. For minor changes to a previously approved protocol during the period covered by the original approval, it may be possible for the Investigator to obtain an expedited review by the IEC as allowed.

As part of the IEC requirements for continuing review of approved studies, the Investigator will be responsible for submitting periodic progress reports to the IEC (based on IEC requirements), at intervals appropriate to the degree of study participant risk involved, but no less than once per year. The Investigator should provide a final report to the IEC following study completion.

UCB (or its representative) will communicate safety information to the appropriate regulatory authorities and all active Investigators in accordance with applicable regulatory requirements.

The appropriate IEC will also be informed by the Investigator or the Sponsor, as specified by the applicable regulatory requirements in each concerned country. Where applicable, Investigators are to provide the Sponsor (or its representative) with evidence of such IEC notification.

13.4 Study participant privacy

UCB staff (or designee) will affirm and uphold the study participant's confidentiality. Throughout this study, all data forwarded to UCB (or designee) will be identified only by the study participant number assigned at Screening.

The Investigator agrees that representatives of UCB, its designee, representatives of the relevant IEC, or representatives of regulatory authorities will be allowed to review that portion of the study participant's primary medical records that directly concerns this study (including, but not limited to, laboratory test result reports, ECG reports, admission/discharge summaries for hospital admissions occurring during a study participant's study participation, and autopsy reports for deaths occurring during the study).

13.5 Protocol amendments

Protocol changes may affect the legal and ethical status of the study and may also affect the statistical evaluations of sample size and the likelihood of the study fulfilling its primary objective.

Significant changes to the protocol will only be made as an amendment to the protocol and must be approved by UCB, the IEC, and the regulatory authorities (if required), prior to being implemented.

14 FINANCE, INSURANCE, AND PUBLICATION

Insurance coverage will be handled according to local requirements.

Finance, insurance, and publication rights are addressed in the Investigator and/or CRO agreements, as applicable.

15 REFERENCES

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16 DECLARATION AND SIGNATURE OF INVESTIGATOR

I confirm that I have carefully read and understood this protocol and agree to conduct this clinical study as outlined in this protocol, according to current Good Clinical Practice and local laws and requirements.

I will ensure that all subInvestigators and other staff members read and understand all aspects of this protocol.

I have received and read all study-related information provided to me.

The objectives and content of this protocol as well as the results deriving from it will be treated confidentially, and will not be made available to third parties without prior authorization by UCB.

All rights of publication of the results reside with UCB, unless other agreements were made in a separate contract.

Investigator:

Printed name	Date/Signature

17 SPONSOR DECLARATION

I confirm that I have carefully read and understand this protocol and agree to conduct this clinical study as outlined in this protocol and according to current Good Clinical Practice.

An open-label, fixed-sequence study in healthy study participants to evaluate the effect of coadministered erythromycin on the PK and safety of PSL

ELECTRONIC SIGNATURES

Signed by	Meaning of Signature	Server Approval Date (dd-mon-yyyy (HH:mm))
[redacted]	Clinical Approval	26-Jan-2018 11:51 GMT+01
[redacted]	Clinical Approval	26-Jan-2018 12:03 GMT+01
[redacted]	Clinical Approval	26-Jan-2018 12:14 GMT+01